Neurochemistry in Sleep and its Clinical Manifestations

Catherine Kier, MD
Professor of Clinical Pediatrics
Division Chief, Pediatric Pulmonary, and Cystic Fibrosis Center
Director, Pediatric Sleep Disorders Center
SUNY Stony Brook
No disclosures
Objectives:

At the end of this session, the participant would be able to:

1. Demonstrate that multiple hormones and neurochemicals are regulated during sleep

2. Identify and relate the clinical manifestations of multiple bodily functions such as growth, learning, memory to sleep promotion and deprivation
Why do we sleep?

- To rest
- To restore exhausted brain metabolism
- LIMITED VIEW
- complex processes that occur in the sleeping brain
With altered sleep...

- Cancer
- Weight gain
- Inflammation
- Depression
- Harder to control emotions
- Harder to read other people’s emotions (relationships)
- Weakens immune system
- Increases risk of diabetes
With altered sleep... (2)

- Permanently damages your skin (collagen)
- Makes your brain dirty
  (sleep promotes removal of neural waste from brain)
- Decreases life expectancy
- Reduces effects of vaccines
- Increases risk of heart disease
- Tricks you (judging effectiveness at basic tasks)
With altered sleep... (3)

• Increases blood pressure
• Irregular heart beats
• Increases risk of stroke
• Makes you weaker (muscle mass)
• Destroys your bones (body cannot repair itself)
• Increases chronic pain
With altered sleep... (4)

• Decreases ability to cope with stress
• Decreases ability to respond under pressure (panic and rushed decision)
• Kills creativity
• Increases risk in dying from car accident
• Causes memory loss
Why do we sleep?

- physiological function of sleep
- contributes significantly to learning and memory
- Neuroplasticity
  - connections among neuronal networks for consolidation in the hippocampus
  - behavior, environment, thinking, emotions, recovery (e.g. changes from bodily injury)

Various areas of the brain

• For episodic memory
  • Hippocampus
  • Medial temporal lobe structures
• Neocortical areas for long-term storage
Sleep is an active phenomenon
Sleep cycles

Stages of Sleep

- **NREM** (75% of night)
  - **Stage 1**
    - Between being awake and falling asleep
    - Light sleep
  - **Stage 2**
    - Onset of sleep
    - Disengaged from surroundings
    - Regular respiratory and heart rate
    - Body temperature drops

National Sleep Foundation, accessed 2015
Stages of Sleep (2)

• **Stages 3 and 4**
  • Deepest and most restorative
  • Blood pressure drops
  • Breathing becomes slower
  • Muscles are relaxed
  • Blood supply to muscles increases
  • Tissue growth and repair occurs
  • Energy is restored
  • Growth hormone released
Stages of Sleep (3)

• **REM** (25% of night)
  • occurs about 90 minutes after sleep
  • recurs about every 90 minutes;
  • getting longer later in the night
  • provides energy to brain and body
  • supports daytime performance
  • brain is active and dreams occur
  • rapid eye movement
  • muscles are turned off
Sleep may be a privileged time window

- free of interference from external sensory inputs
- allows the brain to consolidate newly acquired information

Consequences of sleep loss

- Experimental animal studies and human studies
  - Similarities but also distinct differences
  - Offer insight into the function of sleep
- largely species specific
- Predator versus prey
  - birds - no lengthy bouts of REM sleep
- Unihemispheric SWS
  - one cerebral hemisphere shows waking while the other shows SWS activity
Deficits in cognitive function

• Consequence of sleep loss
  • Sleep disordered breathing (obstructive sleep apnea)
  • Social and occupational demands (e.g. to increase productivity)
• Especially detrimental when sleep loss is chronic
  • Disruption in the learning and memory processes at the cellular level
Sleep loss

• inhibit hippocampal cell proliferation and therefore, inhibit neurogenesis (processes in learning and memory)
• oxidative stress impair neurogenesis (antioxidants can reverse this effect)

Pro-inflammatory effects of sleep loss

• compromise immune function
• increased cytokine secretion
  • IL-1, tumor necrosis factor (TNF), IL-6, C-reactive protein (CRP)
Noninvasive Imaging of Brain Oxygen Metabolism

• Nocturnal enuresis
  • closely related to hypoxia in children with primary nocturnal enuresis (PNE)

• Neurological evaluation, structural imaging, phase-contrast, and the TRUST MRI method
  • high oxygen consumption could make PNE children more susceptible to hypoxia

TRUST MRI T2-relaxation-under-spin-tagging magnetic resonance imaging technique

Neurogenesis

• life long process
  • newborn neurons continue to mature and integrate in the functional network of the dentate gyrus
• Adult neurogenesis in certain areas of the brain
• impairment in these processes may lead to pathogenesis of neuropsychiatric and neurodegenerative disorders

Hormones affected...

- Cancer
- Weight gain
- Inflammation
- Depression
- Harder to control emotions
- Harder to read other people’s emotions (relationships)
- Weakens immune system
- Increases risk of diabetes

- Leptin/ghrelin
- Cytokines
- Serotonin
- Cytokines
- Insulin
Hormones affected... (2)

- Permanently damages your skin (collagen)
- Makes your brain dirty (sleep promotes removal of neural waste from brain)
- Decreases life expectancy
- Reduces effects of vaccines
- Increases risk of heart disease
- Tricks you (judging effectiveness on basic tasks)

Cortisol
Cytokines
Catecholamines
Hormones affected... (3)

- Increases blood pressure
- Irregular heart beats
- Increases risk of stroke
- Makes you weaker (muscle mass)
- Destroys your bones (body cannot repair itself)
- Increases chronic pain

- Norepinephrine
- Catecholamines
- Growth hormone
- Serotonin
Hormones affected... (4)

- Decreases ability to cope with stress
- Decreases ability to respond under pressure (panic and rushed decision)
- Kills creativity
- Increases risk of dying in car accident
- Causes memory loss
Two processes: Homeostatic and circadian drive
High alertness 10:00
Highest testosterone secretion 09:00
Bowel movement likely 08:30
Melatonin secretion stops 07:30
Sharpest rise in blood pressure 06:45
Lowest body temperature 04:30
Deepest sleep 02:00
Midnight 00:00
Noon 12:00
Best coordination 14:30
Fastest reaction time 15:30
Greatest cardiovascular efficiency and muscle strength 17:00
18:00
18:30 Highest blood pressure
19:00 Highest body temperature
21:00 Melatonin secretion starts
22:30 Bowel movements suppressed
Neurochemistry

- Acetylcholine
- Noradrenaline
- Serotonin
- Histamine
- Dopamine
- Glutamate and GABA
- Hypocretin/orexin
Neurochemical changes associated with stress-induced sleep disturbance in rats

• Animal studies
  • to understand the alteration in the cerebral neurochemical profile
  • to determine factors that cause bioalteration in rats subjected to sleep-induced disturbance (SSP rat)

• Concentrations of glutamine (Gln), serotonin (5-HT), and dopamine (DA) exhibited a significant negative correlation in the SSP rat

*Plos ONE, 2016. 11(4). doi:10.1371*
Noradrenaline (norepinephrine)

• modulation of vigilance
• Amphetamine: enhances catecholamine release and prevents reuptake → arousals
• Sleep deprivation with depletion of catecholamines in humans → severe cognitive impairment

Serotonin

- Central neurotransmitter
- Sleep/wakefulness
- Pain perception
- Synthesized by pineal gland
- Behavior and neuroendocrine regulation
Melatonin and serotonin

Serotonin → N-acetylserotonin → Melatonin

serotonin-N-acetyltransferase → hydroxyindole-O-methyltransferase

Dopamine Pathways
- Frontal cortex
- Striatum
- Substantia nigra
- Nucleus accumbens
- VTA
- Hippocampus
- Raphe nuclei

Functions
- Reward (motivation)
- Pleasure, euphoria
- Motor function (fine tuning)
- Compulsion
- Perseveration

Serotonin Pathways
- Mood
- Memory processing
- Sleep
- Cognition
Melatonin secretion

Melatonin levels peak in the middle of the night.

Melatonin production increases in the evening.

Melatonin levels fall to normal daytime levels by early morning.
Melatonin across ages

Fig. 1. Age-related decrease in hormone production in humans.
Melatonin on autism disorders

• serotonin-melatonin pathway as a biomarker for autism spectrum disorders (ASD)

• Hyperserotonemia and the melatonin deficit in ASD in several studies

• increase of the intermediate metabolite N-acetylserotonin in platelets of patients with ASD.

Translational Psychiatry (2014) 4, e479
Cortisol
Cortisol in sleep

• hypothalamic-pituitary-adrenal (HPA) axis
• Cortisol-sleep connection
• dysfunctional HPA (→ alterations in the rhythm of cortisol production) as a basis for understanding cases of insomnia
• reducing cortisol levels and stabilizing HPA axis dysfunction can be a very effective approach to addressing sleep disturbances

Natural Med Journal June 2010; 2(6)
Relationship of melatonin and cortisol
24 Hour GH Secretion
(Growth hormone)
Physiology of growth hormone secretion during sleep

- Growth hormone (GH) pulses during sleep coincide with sleep wave sleep (SWS) and correlates with the concurrent amount of SWS.
- During fourth decade of life (ages 30 to 40 years) the total amount of GH secreted over a 24-hour span decreases by two- to threefold.

Leptin and ghrelin
Sleep duration and weight gain

- Epidemic of obesity with parallel growth in chronic sleep deprivation
- Decreased levels of leptin (a hormone that suppresses appetite) and increased levels of ghrelin (a hormone that stimulates appetite) are associated with short sleep duration in humans

Countering the effects of sleep deprivation – available studies

• Creatine
• Caffeine
• Magnesium
• Tyrosine
• Phosphatidylserine
• Naps
• Exercise
• Meditation
Countering the effects of sleep deprivation

• Nicotine
  • attenuate the impairment of learning and memory associated with several mental disorders including Alzheimer’s disease and chronic psychosocial stress

• Caffeine
  • low doses have positive effects on learning and memory
  • Chronic caffeine intake shown to alleviate cognitive impairment in different animal models of brain disorders
Countering the effects of sleep deprivation (2)

- Physical exercise
  - Nonpharmacological
  - Attenuate memory impairment in a variety of conditions including brain injury
- Enhance cognitive function
- Prevent memory decline in aging
- Decrease anxiety related behaviors
- Attenuate oxidative stress

Current Neuropharmacology, 2013, 11, 231-249
Pharmacotherapeutic approaches for insomnia

- Sedation of historic insomnia medications was discovered serendipitously.
- Now compounds can be developed for specific molecular targets with known sleep-related actions.
- Innovative sleep-promoting medications such as suvorexant and tasimelteon:
  - Suvorexant through antagonism of orexin receptors.
  - Tasimelteon as selective agonist for melatonin receptors.
Pharmacotherapeutic approaches for insomnia

• Current FDA-approved insomnia treatment medications are:
  • benzodiazepine receptor agonists
    • available in immediate-release, extended-release, and alternative delivery oral absorption formulations
  • a melatonin receptor agonist
  • a histamine receptor antagonist
Alternative approaches to treating insomnia

• included prescription medications on an off-label basis for insomnia, over-the-counter sleep aids, and assorted unregulated substances marketed to enhance sleep
• a central nervous system stimulant of the methylxanthine class
• Adenosine antagonist
• Promotes wakefulness by blocking adenosine (sleep-promoting peptide)
• Also causes release of stress hormones (such as cortisol)
Coffee!!!!!!

• caffeine prior to nocturnal sleep increases sleep latency and reduces sleep efficiency

• morning caffeine ingestion decrease sleep efficiency and overall sleep during the subsequent night

Brain Res 1995;675:67–74
“Energy drinks”

- Palpitations / tachycardia
- Tremor / shaking
- Agitation / restlessness
- Gastrointestinal upset
- Chest pain/ischemia
- Dizziness/syncope
- Paresthesia (tingling or numbing of the skin)
- Insomnia
- Respiratory distress
- Headache
Energy drinks: health risks and toxicity

• 297 exposures to energy drinks (217 subjects)
• increasing annual trend from 12 in 2004 to 65 in 2010
• Median age 17 years
• 57% were male
• 21 subjects with serious cardiac or neurological toxicity, including hallucinations, seizures, arrhythmias or cardiac ischemia
• 128 subjects (57 with no co-ingestants) required hospitalization

Alcohol and sleep

• Moderate alcohol consumption lowered restorative sleep quality by 24%, and high alcohol intake by as much as 39.2%
• Affects circadian rhythm
• Blocks REM sleep
• Increases upper airway collapsibility
• Decreases natriuretic peptide
### Sedatives, antidepressants and opiates

<table>
<thead>
<tr>
<th>SSRIs</th>
<th>Opiates</th>
<th>Benzodiazepines</th>
<th>Tramadol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduce REM sleep</td>
<td>Block access to REM</td>
<td>Increase Stage 2 sleep</td>
<td>Increase stage 2</td>
</tr>
<tr>
<td>Increase latency into REM sleep</td>
<td>Stage 3 &amp; 4 sleep</td>
<td>Reduce 3 &amp; 4 esp. after repeated doses</td>
<td>Decrease Stage 3 &amp; 4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Increase Sigma activity</td>
<td>Decrease REM</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reduce latency to sleep</td>
<td></td>
</tr>
</tbody>
</table>
Opiates

• used to treat acute and chronic pain
• But one side effect of opioids is sleep disruption which, in turn, exacerbates pain
• healthy humans:
  • a single intravenous infusion of morphine decreases stages 3 and 4 NREM sleep, decreases REM sleep, and increases stage 2 NREM sleep
  • a nighttime dose of morphine or methadone decreases stages 3 and 4 NREM sleep while increasing stage 2 NREM sleep
  • cycle of opioid-induced sleep disruption leading to increased pain and increased opioid requirement is recognized as a significant clinical problem that must be addressed

Summary:

- Multiple hormones and neurochemicals are regulated during sleep with overlapping and intricate interactions.

- Growth, learning, memory are deeply related to sleep promotion and deprivation.

- Numerous fascinating studies, leading to potential targets of pharmacological (neurochemicals) and non-pharmacological approaches (lifestyle modifications).