Neurochemistry in Sleep and its Clinical Manifestations

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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

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
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Hormones affected... (2)

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Cortisol
Cytokines
Catecholamines
Hormones affected... (3)

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Cortisol

Neuroplasticity
Two processes:
Homeostatic and circadian drive
Highest testosterone secretion at 10:00
Bowel movement likely at 08:30
Melatonin secretion stops at 07:30
Sharpest rise in blood pressure at 06:45
Lowest body temperature at 04:30
Deepest sleep at 02:00
Noon at 12:00
Best coordination at 14:30
Fastest reaction time at 15:30
Greatest cardiovascular efficiency and muscle strength at 17:00
Highest blood pressure at 18:30
Highest body temperature at 19:00
Melatonin secretion starts at 21:00
Bowel movements suppressed at 22:30
Midnight at 00:00
Stony Brook Children's
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

Sleep Med Rev 2003 Feb;7(1):101-2;
Melatonin and serotonin

Serotonin

N-acetylserotonin

Melatonin

Dopamine Pathways

Serotonin Pathways

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

Functions
- 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 low 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
STRESS HORMONES

- Breathing rate increases
- Blood flow to skeletal muscles increases
- Heart rate increases
- Blood sugar levels increase
- Blood pressure in arteries increases
- Intestinal muscles relax
- Pupils dilate
Cortisol

![Graph showing cortisol levels throughout the day](https://via.placeholder.com/150)

- **6am to 9am**: Accelerating Activity
- **9am to 12pm**: Decelerating Activity
- **12pm to 3pm**: Wind Down
- **3pm to 6pm**: Physical Repair
- **6pm to 9pm**: Psychological Repair
- **9pm to 12am**: Asleep
- **12am to 6am**: Awake
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
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
Leptin and ghrelin

• Leptin
  • a mediator of long-term regulation of energy balance, suppressing food intake and thereby inducing weight loss

• Ghrelin
  • fast-acting hormone, role in meal initiation

• obese subjects
  • hormone leptin is increased - anorexigenic
  • hormone ghrelin is decreased - orexigenic
  • But established-obese patients are leptin-resistant
Sleep duration and weight gain

• Epidemic of obesity with parallel growth in chronic sleep deprivation

• Society: demands and diet
  • influence on leptin and ghrelin secretion and functioning

• potentials of leptin and ghrelin as drug targets

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
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).