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
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

_Nat. Rev. Neurosci., 2010, 11, 114-26._
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 has been found to be closely related to hypoxia in children with primary nocturnal enuresis (PNE)

• Through neurological evaluation, structural imaging, phase-contrast, and the TRUST MRI method, evidence has been found suggesting that high oxygen consumption and high OEF values could make PNE children more susceptible to hypoxia
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)

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

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Cortisol

Neuroplasticity
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

• To better understand the alteration in the cerebral neurochemical profile, a study was done to determine factors that cause bio alteration in rats subjected to sleep-induced disturbance

• Concentrations of Gln, 5-HT, and DA exhibited a significant negative correlation in the SSP rat data
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

**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**

**Functions**
- Mood
- Memory processing
- Sleep
- Cognition

**Chemical Structures**
- Serotonin
- N-acetylserotonin
- Melatonin

**Enzymes**
- Serotonin-N-acetyltransferase
- Hydroxyindole-O-methyltransferase
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
Stress hormones

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

![Graph showing cortisol levels over a 24-hour period]

- **AWAKE**
  - 6am - 9am: Accelerating Activity
  - 9am - 12pm: Decelerating Activity
  - 12pm - 3pm: Wind Down
  - 3pm - 6pm: Physical Repair
  - 6pm - 9pm: Psychological Repair

- **ASLEEP**
  - 9pm - 12am
  - 12am - 3am
  - 3am - 6am

Stony Brook Children's
Cortisol in sleep

• hypothalamic-pituitary-adrenal (HPA) axis
• Cortisol-sleep connection
• dysfunctional HPA and 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

Clock Time

GH (ng/ml)
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
  • now 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 will be discussed

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

• While the sedation of historic insomnia medications was discovered serendipitously, now compounds can be developed for specific molecular targets with known sleep-related actions.

• The FDA is reviewing new applications for innovative sleep-promoting medications currently, including suvorexant and tasimelteon.
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; and a histamine receptor antagonist.

• Alternative approaches to treating insomnia have included prescription medications employed 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, with numerous fascinating studies, leading to potential targets of pharmacological (neurochemicals) and non-pharmacological approaches (lifestyle modifications)