The Science of Wellness: Why Your Doctor Continues to Insist You Sleep and Exercise to be Well

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Sleep Cycle

- Spend 1/3 of our time in sleep
- Two types of Sleep
  - Non-rapid eye movement (NREM)
    - 75-80% of sleep
    - Stages 1-4
  - Rapid eye movement (REM)
    - 20-25% of sleep
    - Stage 5
- Cycle between NREM and REM several times a night, lasting 70-100mins initially, then 90-120mins
EEG wave form

Awake

Sleep stage 1

Sleep stage 2

Sleep stage 3

Sleep stage 4

Sleep stage 5 (REM)
Stage 1

- 2-5% total sleep
- Rhythmic alpha waves to low-voltage frequency seen in wakefulness
- Transitional stage, easily interrupted
- Lasts only 1-7 minutes in the initial cycle
Stage 2

- 45-55% of sleep
- Lasts 10-25 mins initially and lengthens with each successive cycle
- Deeper sleep, requiring more intense stimuli to waken
- Relatively low voltage, mixed frequency with sleep spindles and k-complexes
  - Spindles thought to be important for memory formation
  - Suppress cortisol arousal in response to stimuli
Stages 3 and 4

- “slow wave” or deep sleep occurring in the first third of the night
- Stage 3
  - Lasts only a few minutes making up 3-8% of sleep
  - Increased high voltage, slow wave activity
- Stage 4
  - Lasts approx. 20-40mins in the first cycle, making up 10-15% of sleep
  - Highest arousal threshold
  - Increased amounts of high-voltage, slow wave activity
Stage 5 (REM)

- 20-25% of sleep (longest in last 1/3 of night)
- Length increases as the night progresses
  - Initial lasts 1-5 mins, becomes progressively longer
- Desynchronized (low voltage, mixed frequency) brain wave activity, muscle atonia, bursts of rapid eye movements
- “saw-tooth” wave forms with the theta activity and slow alpha activity
- Dreaming occurs during this stage
  - Loss of muscle tone and reflexes prevents one from acting out dreams
- May also be important for memory formation
Physiology During Sleep

O Cardiovascular
  O Autonomic nervous system regulates blood pressure and heart rate
  O Both are typically higher prior to awakening

O Sympathetic nervous system: decreases as NREM progresses

O Cerebral blood flow
  O Reduction of blood flow and metabolism occurs during NREM
  O Total blood flow and metabolism during REM is comparable to wakefulness, includes limbic system and visual association areas
Physiology During Sleep

- Respiratory
  - Increased rate of respiration and ventilation (REM)
  - Hypoventilation due to reduced pharyngeal muscle tone (NREM)
  - Suppressed cough reflex (REM and NREM)
  - Decreased rib cage movement/increased upper airway muscled (REM)
  - Arousal response to respiratory resistance is lowest in stage 3 and 4
Physiology During Sleep

O Renal
  O decreased excretion of sodium, potassium, chloride, and calcium to concentrate urine
  O Involved with changes in renal blood flow, glomerular filtration, hormone secretion and sympathetic neural stimulation

O Endocrine
  O Growth hormone secretion takes place in the first few hours after sleep onset, occurring during slow wave sleep
  O Thyroid hormone secretion takes place late evening
  O Melatonin induces sleepiness, reducing an altering effect from the suprachiasmatic nucleus, influenced by the light-dark cycle
Sleep-Wake Cycle

- Promotion of sleep (Process S) and maintaining wakefulness (Process C)
- Process S accumulates across the day, peaks before bedtime and dissipates throughout the night
  - Regulated by neurons in the hypothalamus that shut down the arousal system, allowing for sleep
  - Loss of these nerves causes insomnia
- Process C is wake promoting and is regulated by the circadian system
  - Builds across the day
  - Declines at bedtime, serving to enhance sleep consolidation
  - In the absence, total sleep time remains the same, but is randomly distributed over the day and night
Sleep Wake Cycle

- Enough sleep reduces the homeostatic drive for sleep, increases the circadian waking drive, restarting the cycle.
- Also receive input from lower brainstem that relay info about the state of the body, including emotional and cognitive areas of the forebrain.
- Neurons in the pons switch between NREM and REM.
- Neurons send output to the lower brainstem and spinal cord causing muscle atonia, rapid eye movements, and chaotic autonomic activity.
Circadian Rhythm

- Daily rhythm in physiology and behavior
- Controls sleep-wake cycle, modulates physical activity, food consumption, body temp, heart rate, muscle tone and hormone secretion
- Generated by neural structures in the hypothalamus (biological clock)
- Regulated by the suprachiasmatic nucleus (SCN)
  - Receives direct input from brightness detectors in the retina (resets the clock genes in the SCN daily)
  - SCN transmits to the rest of the brain and body signals that synchronize daily cycles with external day-night cycle
Influence of SCN on Sleep

- Series of relays through the dorsomedial nucleus (DMN) in the hypothalamus
  - Signals the wake-sleep system to coordinate activity with the day-night cycle
  - Coordinates cycles of feeding, locomotor activities, and hormones (cortisol)
- Influenced by external environment changes (temperature, stress, limited food)
Biological Clock Function

- 3 components
  - Input from the Zeitgebers in the retina to act on the SCN circadian pacemaker cells
  - Pacemaker cells release neurotransmitters and peptides that act on the pineal gland
  - Pineal gland secretes melatonin, thermoregulation hormones and other hormones
- The above interact with the sleep-wake cycle to modulate sleep propensity and sleep architecture → influence behavior, performance and hormonal output (i.e. cortisol)
HPA Axis
Systemic - Endocrine

Normal Diurnal Rhythm

Stress Cytokines

CRH +ve

+ve

Hypothalamus

Feedback

Pituitary

ACTH +ve

Feedback

Adrenal

Cortisol (Hormonally Active)
Effects of Age on Sleep Patterns

- Sleep provides different needs at different times in your life
- Sleep architecture changes
- Sleep efficiency declines with age
Birth to 3 months

- Circadian rhythm hasn’t fully developed
- Sleep time is distributed evenly across the day and nights without regular rhythm or concentration of sleeping/waking
- No true NREM and REM sleep
  - Quiet sleep (similar to NREM)
  - Active sleep (similar to REM)
  - Indeterminate sleep
- Need 16-18 hours of sleep a day, discontinuous, about 2.5-4 hours at a time
- Sleep onset occurs through active sleep (REM) and each sleep episode consists of only one or two cycles
2-3 months

- Circadian rhythm emerges → sleep consolidation that resembles adult sleep, including cycling of melatonin and cortisol
- Responsive to social cues
- Sleep starts with NREM
- REM decreases and shifts to the later part of the cycle
- Cycles last about 50 minutes
- Muscle paralysis of REM replaces the propensity for movement in “active sleep”
Young Children

- Amount of sleep decreases as children get older (decreased from 13 to 11 hours)
- Reduction influenced by physiological, cultural and social environment
  - Sleep routines
  - Less frequent napping
- Sleep difficulties start; difficulties initiating or maintaining sleep
- Nightmares $\rightarrow$ discontinuous sleep
- Start spending greater time in Stage 3 and 4 with longer REM sleep latencies
Adolescents

- Complex and bidirectional relationship between pubertal development and sleep (? related to hormone changes)
  - Midpuberty there is greater daytime sleepiness
- Total time spent sleeping decreases as age increases
  - Require 9-10 hours of sleep, only average between 7-8 hours
  - REM sleep remains constant if bedtime is fixed
Young Adults

- Sleep remains consolidated
- Brief awakenings, close to REM, often where arousal occurs, as opposed to occurring in NREM as it does with older adults
Adults

- Begin to see an earlier wake time with reduced sleep consolidation
- SWS declines by 2% every decade
- Reduction in homeostatic sleep pressure and circadian pacemaker
- Increased sensitivity to light?
Elderly Adults

- Sleep 36% less than children (age 5)
- Ability to sleep decreases, but need for sleep does not
- Increase in disturbed sleep that negatively affects quality of life, mood, and alertness
- 43% of individuals have difficulty initiating and maintaining sleep
Elderly Adults

- Increased stage 1 and decreased REM
- Decreased melatonin levels
- Decreased homeostasis leads to inability to maintain long sleep episodes and bouts of wakefulness
- Increased sleep latency, nighttime wakening and inconsistency of external cues (light exposure), irregular mealtimes, nocturia, and decreased mobility often leading to reduced exercise
- Affects males and females differently
Older Females

- Maintain SWS longer
- Spend 15-20% of sleep in stages 3 and 4
- Tend to go to bed and wake earlier; ? Body temp rhythms may be more advanced in women
- Harder time falling asleep and maintaining sleep
Older Males

- Spend only 5% of sleep in stages 3 and 4
- Decreased SWS
- Spend more time in stage 1 sleep and experience more frequent awakenings
- More likely to complain of daytime sleepiness
Hypothalamic-Pituitary-Adrenal (HPA) Axis

Effects of Stress on Sleep and Cortisol Production
HPA Role in Sleep and Stress

- Modulates sleep-wake cycle
- Follows a distinct 24 hour pattern
- Influenced by sleep loss, resulting in hyperactivation
HPA Axis

- Hypothalamus resides in the base of the brain
  - Produces a hormone called CRH, which acts on the pituitary gland
- Pituitary gland resides at the base of the brain
  - Produces several hormones that act on various organs
  - Produces ACTH, which acts on the adrenal cortex of the adrenal glands
- Adrenal glands reside above the kidneys and produce several hormones, including cortisol and epinephrine (adrenaline)
Cortisol, Sleep Deprivation, and Stress

- Increased cortisol levels during the nighttime period during sleep deprivation and prolonged wakefulness of the following day
  - Likely the results of efforts of maintaining wakefulness
- Elevated cortisol $\rightarrow$ impairment of HPA axis $\rightarrow$ glucocorticoid overload $\rightarrow$ deleterious effects on body (obesity, DM2, metabolic syndrome)
- Elevated glucocorticoids $\rightarrow$ increased time spent awake $\rightarrow$ less time in REM
Sleep Duration and Obesity

- Short sleep duration may be a predictor of weight gain and increase risk for insulin resistance, diabetes, and cardiovascular disease.
- Each reduction of 1 hour of sleep per day is associated with an increase of 0.35 in BMI.
- Imbalance between food intake and energy expenditure.
  - Sleep is a period of fasting.
  - Glucose utilization by the brain is increased in REM and at the end of the night.
  - Sleep “resets” metabolism and energy expenditure in the brain.
Appetite and Sleep

- Appetite promoting neuropeptide Y (NPY) and agouti-related protein (AGRP) neurons mutually inhibit the appetite suppressing pro-opiomelanocortin (POMC) and amphetamine related transcript (CART) neuron
  - Works as sensors of the circulating hormones leptin and ghrelin
Leptin

- Produced by adipose tissues
- Promotes satiety by inhibiting NYP/AGRP and activating POMC/CART
- Higher levels during sleep
- May reduce REM sleep and modulate SWS
Ghrelin

- Appetite stimulating hormone produced in the gut
- Inhibits POMC/CART and activates NYP/AGRP
- Higher during sleep
- Decreased in AM before breakfast
- Sleep promoting by inducing SWS and stimulating growth hormone (GH) overnight
Affects of Sleep on Leptin and Ghrelin

- Decreased sleep → decreased leptin + increased ghrelin → increased food intake
  - Two consecutive nights (4 hours of sleep) in young men were associated with a 28% increase in ghrelin and 18% reduction of leptin, leading to increased hunger and appetite, mostly for energy rich foods (high carbs, salty, sweet, starch)
  - Six consecutive nights increased sympathetic nervous system activity, evening cortisol levels and growth hormone, decreased glucose effectiveness and acute insulin response by 30% (comparable to a non-insulin dependent diabetic)

- Restriction in energy expenditure
  - Less sleep promotes fatigue and sleepiness during the day, which may reduce daytime activities and promote sedentary lifestyle
Stress and Metabolism

- Prolonged activation of the HPA axis results in maladaptive changes, affecting puberty, stature, body composition, which can lead to obesity, metabolic syndrome and type 2 diabetes.
- Increased glucocorticoids increase glucose and insulin and decrease adiponectin levels.
- Alters food intake (stimulated appetite by steroids), rewards based eating (to decrease stress response).
- Unclear how cortisol affects pathology of obesity, but has been shown to contribute to the development of metabolic syndrome.
Physiological Effects of Exercise on Your Body
• Reduces causes of mortality by up to 30%
  • Seen consistently across all age groups and racial/ethnic minorities
• Lowers prevalence of chronic disease
• Improves one’s self-esteem and sense of wellbeing
• Slows rate of age-related memory and cognitive decline
• Fewer depressive and anxiety symptoms
- Effects are dependent on the type of training and exercise you do
- Changes take time, typically 4-8 weeks
- Adaptive changes disappear when you stop exercising
How the Heart Adapts

- Increase in cardiac output by increasing heart rate and stroke volume
  - Increased force of contraction
  - Greater emptying of the heart chamber
- Enlargement of the left ventricle
- More blood, more oxygen available to exercising muscles
- As muscles train they become better able to extract and use oxygen to produce more work
How the Circulatory System Adapts

- Blood flow is redistributed
  - Less blood to all major organs except the heart and brain
  - More blood flow to muscles and skin
- Arteries dilate in the working muscles and blood flow increases through capillaries
  - Increases the exchange of oxygen, the release of heat and removal of metabolic waste (lactic acid, carbon dioxide)
How the Circulatory System Adapts

- Secretion of hormones and signaling dilation of blood vessels in the heart and working muscles
- Secretion of hormones in inactive tissues for constriction of blood vessels
  - Increase redistribution of blood
- Increase in the number of capillaries in muscles
- Blood becomes thinner, allowing better flow through capillaries
  - More water and dissolved proteins are added to the plasma volume
How Muscles Adapt

- Muscle oxygen consumption increases up to 70 times above resting volumes.
- Capillary density increases up to 40%, allowing more oxygen, nutrients, and hormones to be delivered, stimulating better removal of heat.
- Better use of oxygen to produce work and improves ability to store glycogen.
  - Converted to ATP (energy).
Effects on the HPA Axis

- Acute stress leads to alterations in ACTH and excess levels of glucocorticoids
- Chronic stress has been associated with lower concentrations of peripheral cortisol and upregulation of the glucocorticoid receptors resulting in increased feedback sensitivities
- Voluntary exercise alters the release of CRF from the hypothalamus and ACTH from the anterior pituitary
Effects on Serotonin Levels and Endorphins

- Increases serotonergic and noradrenergic levels in the brain
  - Through serotonin synthesis, metabolism and release
- Increases endogenous opioid activity in the CNS and PNS, releasing endorphins and reducing pain
  - Lifts mood and decreases anxiety
References

- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4688585/#bib3
- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3632802/