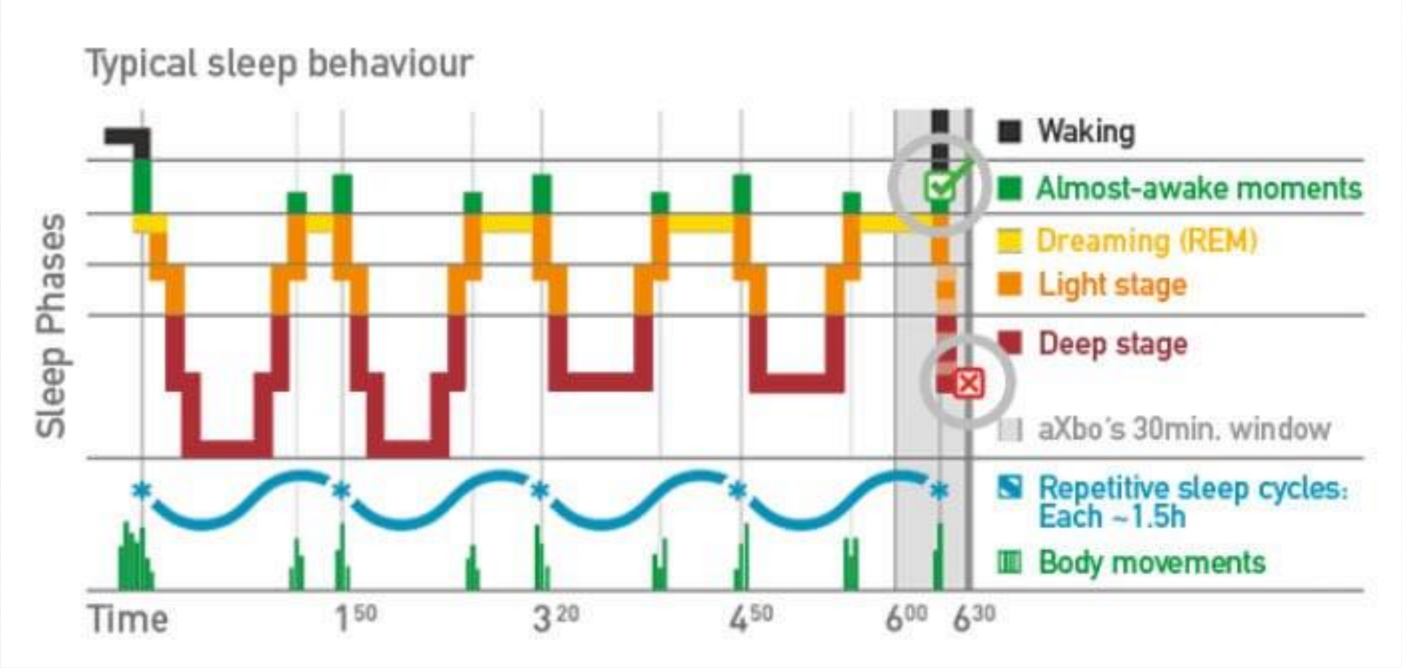
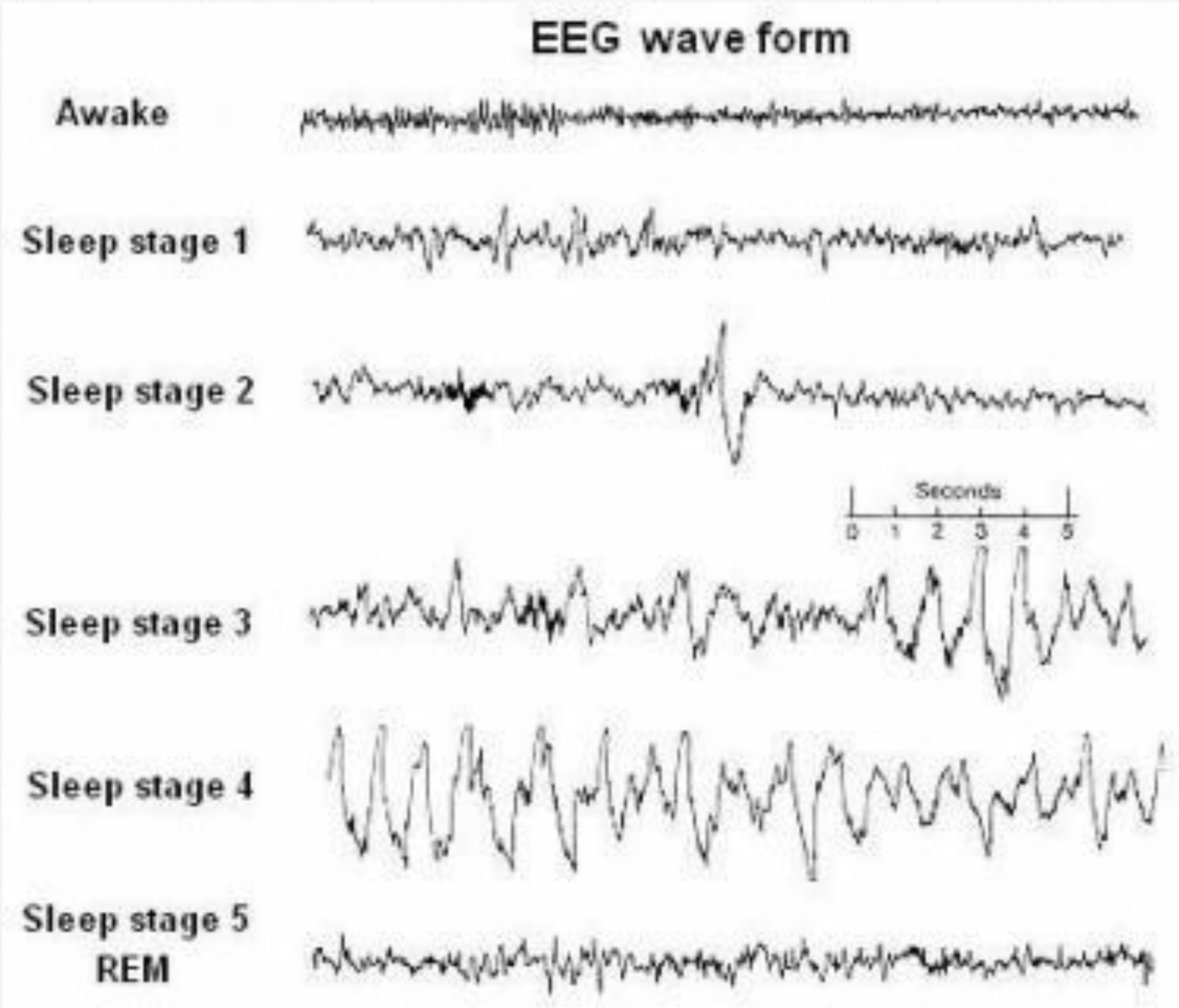
The Science of Wellness: Why Your Doctor Continues to Insist You Sleep and Exercise to be Well

Nicole Rausch, DO

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


Typical sleep behaviour
Sleep Phases
Waking
Almost-awake moments
Dreaming (REM)
Light stage
Deep stage
aXbo's 30min. window
Repetitive sleep cycles: Each ~1.5h
Body movements
Time
1 50
3 20
4 50
6 00
6 30


EEG wave form
Awake
Sleep stage 1
Sleep stage 2
Seconds
0 1 2 3 4 5
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

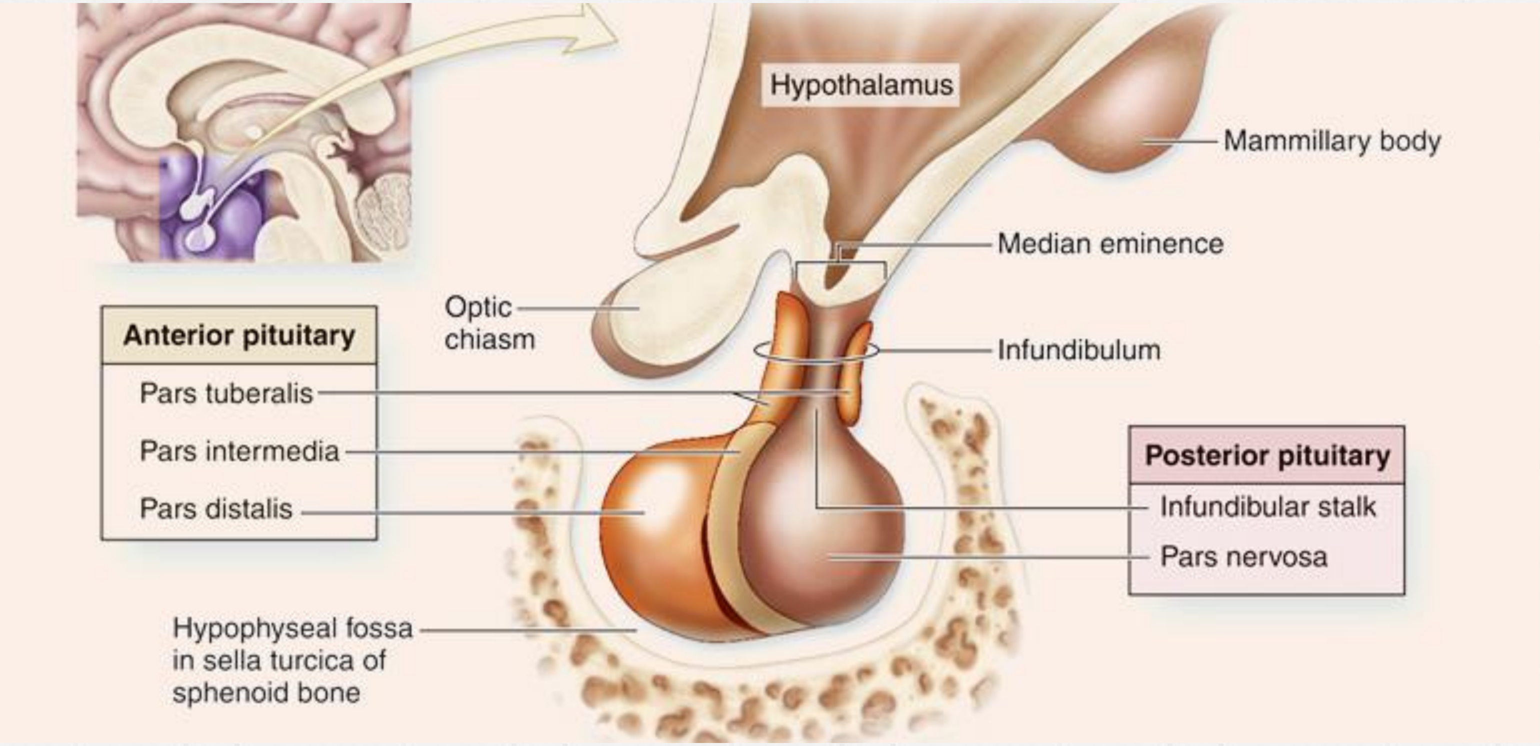
- 45-55% of sleep
- Lasts 10-25 mins initially and lengthens with each successive cycle
- Deeper sleep, requiring more intense stimuli to waken
- Relatively low voltage, mixed frequency with sleep spindles and k-complexes
  - Spindles thought to be important for memory formation
  - Suppress cortisol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



Hypothalamus
Mammillary body
Median eminence
Optic chiasm
Infundibulum
Anterior pituitary
Pars tuberalis
Pars intermedia
Pars distalis
Posterior pituitary
Infundibular stalk
Pars nervosa
Hypophyseal fossa in sella turcica of sphenoid bone

Physiology During Sleep

- Cardiovascular
  - Autonomic nervous system regulates blood pressure and heart rate
  - Both are typically higher prior to awakening
- Sympathetic nervous system: decreases as NREM progresses
- Cerebral blood flow
  - Reduction of blood flow and metabolism occurs during NREM
  - 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

- Renal
  - decreased excretion of sodium, potassium, chloride, and calcium to concentrate urine
  - Involved with changes in renal blood flow, glomerular filtration, hormone secretion and sympathetic neural stimulation
- Endocrine
  - Growth hormone secretion takes place in the first few hours after sleep onset, occurring during slow wave sleep
  - Thyroid hormone secretion takes place late evening
  - Melatonin induces sleepiness, reducing an altering effect from the suprachasmatic 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

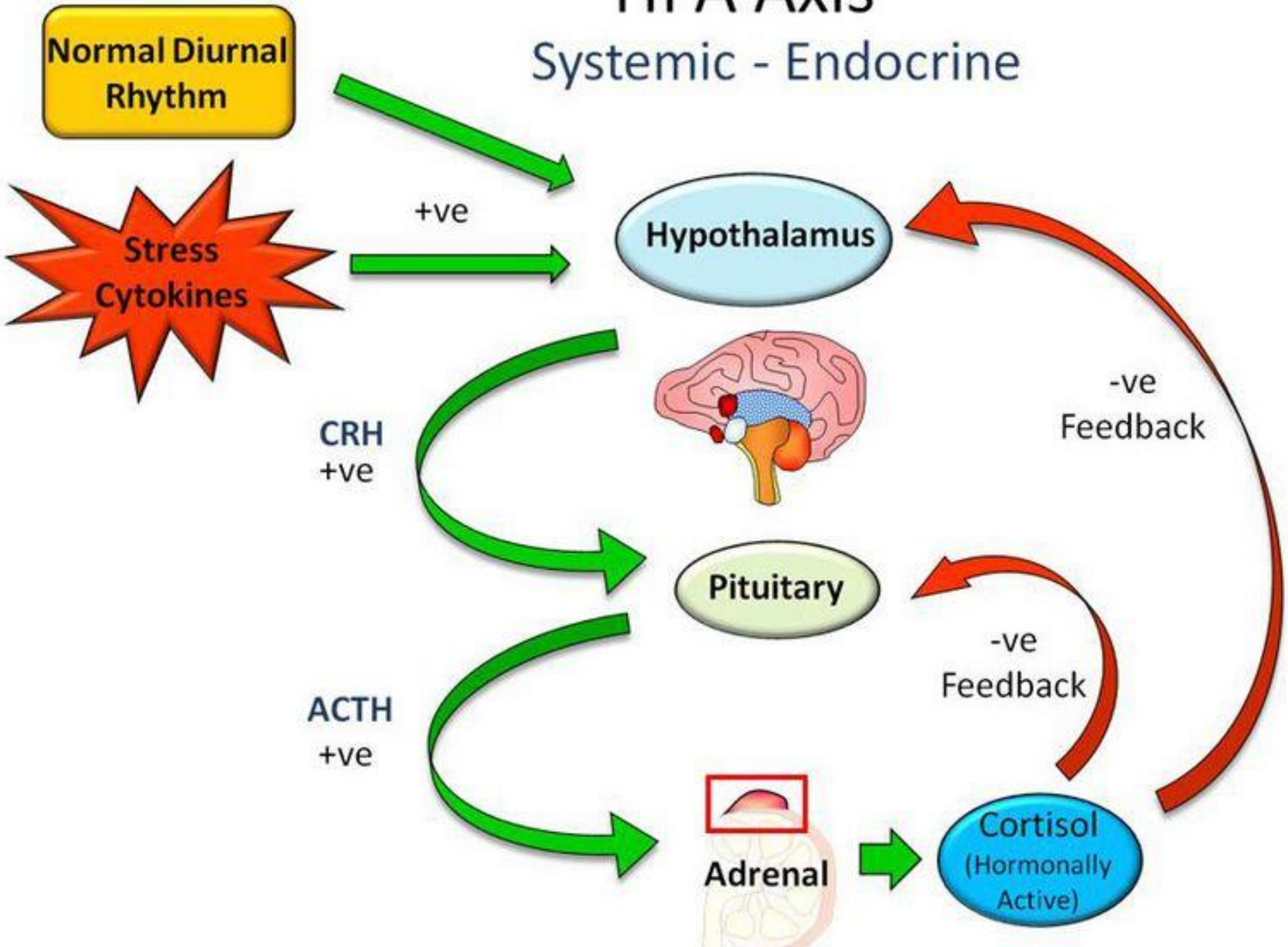
- Series of relays through the dorsomedial nucleus (DMN) in the hypothalamus
  - Signals the wake-sleep system to coordinate activity with the day-night cycle
  - Coordinates cycles of feeding, locomotor activities, and hormones (cortisol)
- Influenced by external environment changes (temperature, stress,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

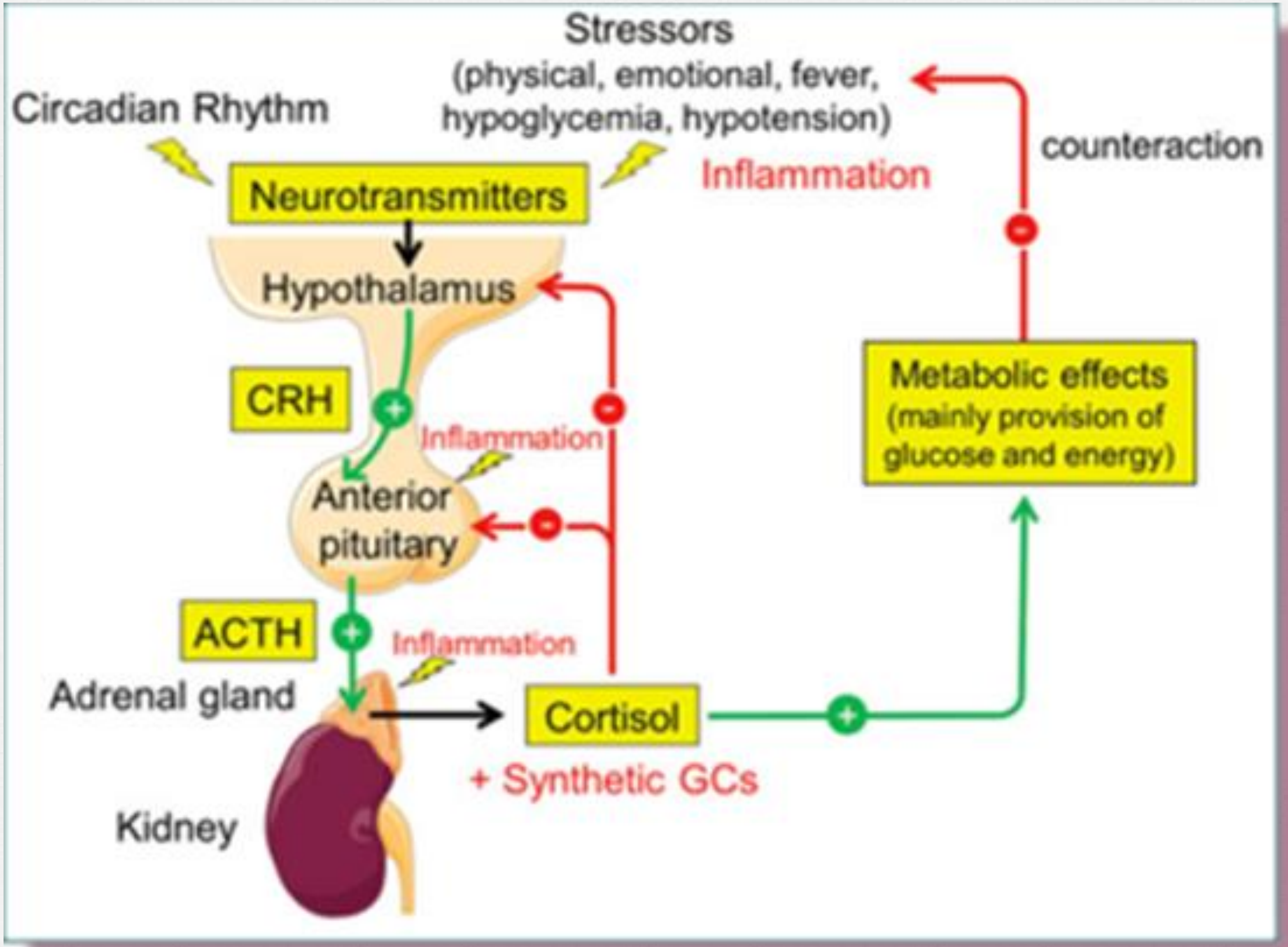
Biological Clock Function

- 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)

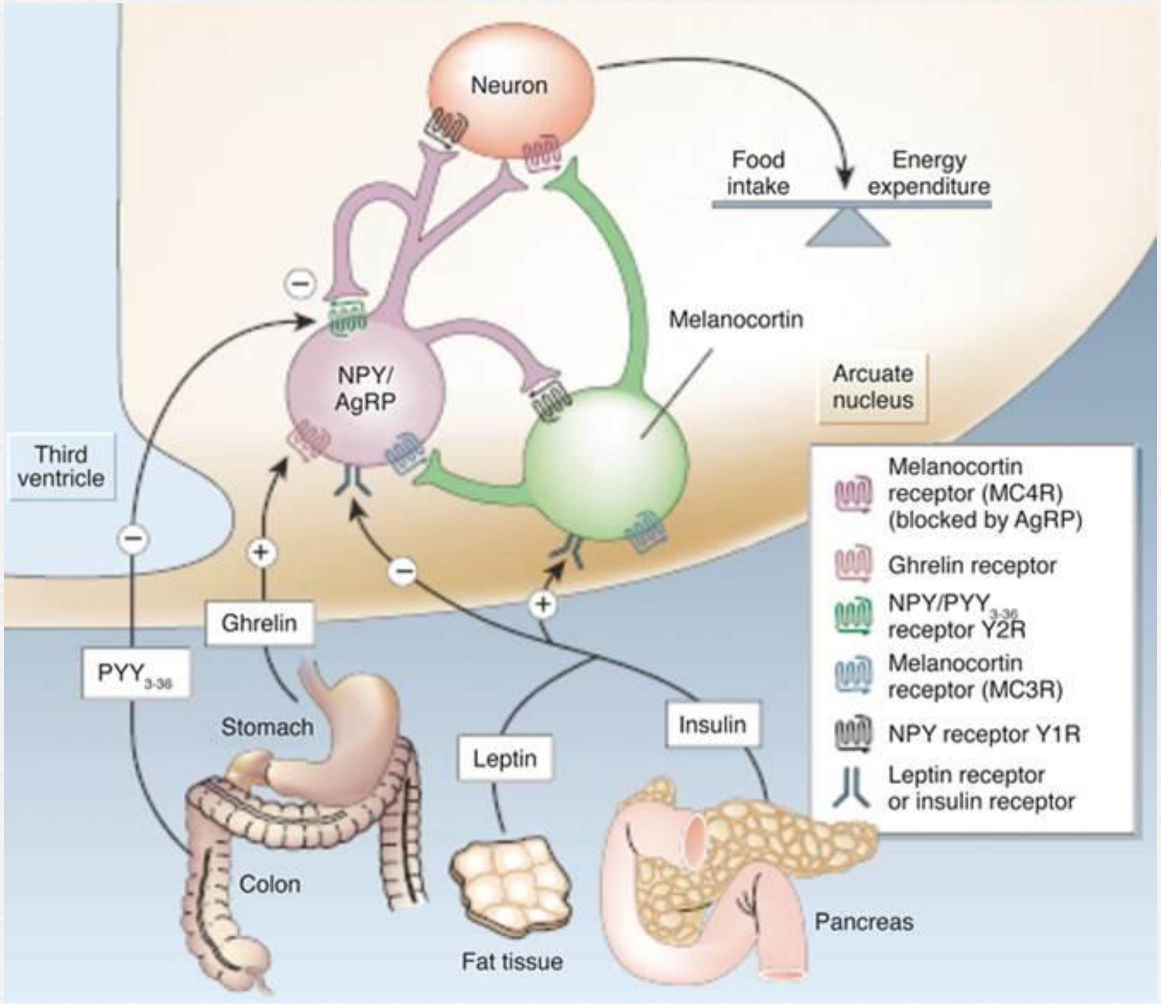
HPA Axis

Systemic - Endocrine





Stressors
(physical, emotional, fever,
hypoglycemia, hypotension)
Circadian Rhythm
counteraction
Inflammation
Neurotransmitters
Hypothalamus
CRH
Inflammation
Anterior
pituitary
Metabolic effects
(mainly provision of
glucose and energy)
ACTH
Inflammation
Adrenal gland
Cortisol
+ Synthetic GCs
Kidney



Neuron
Food intake
Energy expenditure
Melanocortin
Arcuate nucleus
NPY/ AgRP
Third ventricle
Melanocortin receptor (MC4R) (blocked by AgRP)
Ghrelin receptor
NPY/PYY3-36 receptor Y2R
Melanocortin receptor (MC3R)
NPY receptor Y1R
Leptin receptor or insulin receptor
PYY3-36
Ghrelin
Stomach
Leptin
Insulin
Colon
Fat tissue
Pancreas

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 → 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 → impairment of HPA axis → glucocorticoid overload → deleterious effects on body (obesity, DM2, metabolic syndrome)
- Elevated glucocorticoids → increased time spent awake → 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

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