The Science of Circadian Rhythms

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Learning Objectives

- Review the basic concepts of circadian science
- Learn the neurobiology of sleep and circadian rhythms
- Understand the key features of circadian rhythm sleep disorders

Neurobiology of Circadian Rhythms

- Biological rhythms are a fundamental characteristic of life
  - Insufficient cellular energy to perform all functions at the same constant rate and all at the same time
Neurobiology of Circadian Rhythms

- Biological rhythms are ubiquitous
- Found in prokaryotic and eukaryotic microbes, plants, insects and animals, including humans

Neurobiology of Circadian Rhythms

- Biochemical and physiological variables attain peak activity levels at different points in time throughout a circadian period
  - Sleep phase
  - Wake phase
  - Transition between sleep and waking
Lung Function

Moore R et al. Sleep 2006

Spengler C et al. AJRCCM 2000;162;1038-1046
Thermoregulation

- Core body temperature
  - Peaks in the late afternoon and early evening: 6-8 pm
  - Falls at the onset of sleep
  - Nadir at 2 hours prior to usual wake time: 4-5 am

![Graph showing core body temperature with peaks and nadir points.](Baker.FC.et.al.2001)

Sudden Cardiac Deaths

![Bar graph showing percentage of patients by time of day and age group.](Arntz.HR.et.al.Eur.Heart.J.2000.21.315-320)
Circadian Rhythms

- Rhythms are characterized by specific
  - Period (frequency)
  - Amplitude
  - Peak and nadir
  - Phase

Frequency

- Number of oscillations (periods) per unit time
  - *Ultradian* – one oscillation lasting less than 24 hours
  - *Circadian* - one oscillation approximately every 24 hours
  - *Infadian* – one oscillation lasting greater than 24 hours
Ultradian Rhythm

Amplitude

- Maximal excursion from peak to trough
  - Acrophase – peak
  - Mesor – mean
  - Nadir – trough
Phase

- Temporal position in relation to an external cue (e.g., light-dark cycle)
  - *Phase advanced* – shift of an episode to an earlier time in the 24-hour cycle
  - *Phase delayed* – shift of an episode to a later time in the 24-hour cycle
Free Running

- In the absence of environmental time cues, circadian rhythms free-run at slightly over 24 hours ($\approx 24.2$ hours ["tau"])
Entrainment

- Process by which external cues adjust the phase of the intrinsic circadian rhythms
  - Forward or backward
  - Synchronizes the intrinsic circadian cycle to the environmental 24-hour period

Zeitgebers

- Environmental cues that are capable of entraining intrinsic circadian rhythms
- Either *photic* (dominant synchronizer) or *non-photic* stimuli
Light Therapy

- Evening light exposure (before CTmin) ⇒ phase delays circadian rhythms

Phototherapy = phush (pushes sleep away from it)

Evening light

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Melatonin

- Evening melatonin phase advances circadian sleep-wake rhythms

Melatonin = Magnet (pulls sleep towards it)

Evening melatonin
Circadian Timing Systems

- Suprachiasmatic nuclei (SCN) in the anterior hypothalamus
  - Master neural generator of circadian rhythms in mammals
  - Oscillates independently of the environment
    - Fires more frequently during the daytime

Suprachiasmatic Nuclei

<table>
<thead>
<tr>
<th>Actions of SCN</th>
<th>Ablation of SCN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Promotion of wakefulness during the day</td>
<td>Random distribution of sleep throughout the day and night</td>
</tr>
<tr>
<td>Consolidation of sleep during the night</td>
<td>Reduction in duration of waking periods (in some)</td>
</tr>
</tbody>
</table>
### Afferent SCN Pathways

<table>
<thead>
<tr>
<th>Glutamatergic (main)</th>
<th>GABAergic (alternate)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eyes (retina ganglion cells containing melanopsin most sensitive to blue to blue-green light)</td>
<td>Eyes ↓ Thalamic intergeniculate leaflet of the lateral geniculate nuclei ↓ Geniculohypothalamic tract ↓ SCN</td>
</tr>
<tr>
<td>Retinohypothalamic tract ↓ SCN</td>
<td></td>
</tr>
</tbody>
</table>

Moore R et al. Sleep 2006
Genetics of Circadian Rhythms

- Clock genes have been described in cyanobacteria, *Neurospora*, *Drosophila* and mice.
- Mutations in clock genes are associated with faster or slower cycles than normal clocks.

Circadian Rhythm Genes

<table>
<thead>
<tr>
<th><em>Drosophila melanogaster</em></th>
<th>Mammals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Casein kinase 1 (CK1)</td>
<td>B-mal1</td>
</tr>
<tr>
<td>Clock (clk)</td>
<td>Casein kinase 1 (CK1)</td>
</tr>
<tr>
<td>Cryptochrome (cry)</td>
<td>Clock (clk)</td>
</tr>
<tr>
<td>Cycle (cyc)</td>
<td>Cryptochrome (Cry1 and Cry2)</td>
</tr>
<tr>
<td>Period (per)</td>
<td>Period (per1, per2 and per3)</td>
</tr>
<tr>
<td>Timeless (tim)</td>
<td>Timeless (tim)</td>
</tr>
</tbody>
</table>
Genetics of Circadian Rhythms

- Circadian rhythms are controlled by transcription-translation positive and negative feedback loops involving the clock genes and regulatory factors.
Control of Sleep and Waking

- Two basic intrinsic components interact to regulate the timing and consolidation of sleep and wake
  - Sleep homeostasis – dependent on the sleep-wake cycle (sleep promoting)
  - Circadian rhythm – independent of the sleep-wake cycle (alerting)
- Behavioral influences

Control of Sleep and Waking

- Constant alertness throughout the waking period = rising circadian alertness opposing the increase in homeostatic sleep pressure
- Constant sleep throughout the sleep period = falling circadian alerting tendency opposing the decreasing homeostatic sleep
Circadian Rhythm Sleep Disorders

- Caused by a recurrent or persistent misalignment between the desired sleep schedule and the circadian sleep-wake rhythm
- Can be associated with insomnia or excessive sleepiness (or both)

Circadian Rhythm Sleep Disorders

- Delayed Sleep Phase Syndrome
- Advanced Sleep Phase Syndrome
- Irregular Sleep Wake Rhythm
- Free Running Disorder
- Jet Lag
- Shift Work Disorder
Evaluation

- Sleep diaries
- Actigraphy
- Circadian rhythm markers

Actigraphy

- Accelerometers typically worn on the wrist
- A signal is produced whenever movement is detected
- Discerns periods of rest/sleep or activity
- Can be recorded over several days to weeks
Biological Markers

- Two biological markers used to estimate the timing of circadian rhythms
- Dim light melatonin onset (DLMO)
  - Time when melatonin levels start to rise
  - 2-3 hours before bedtime
- Minimum of the core body temperature (CTmin)
  - 2-3 hours before waketime

Delayed Sleep Phase Disorder

- “Night owl”
- Major nocturnal sleep period occurs later than the conventional or socially acceptable bedtime
- Late bedtime (1-6 am) and late wake time (10 am to 2 pm)
DSPD: Therapy

- Chronotherapy
  - Progressive phase delay
  - Progressive phase advancement
  - Scheduled shift technique
- Phototherapy
- Pharmacotherapy
- Maintenance therapy
Chronotherapy

Progressive phase delay
- Bedtime and wake times are delayed by about 2-3 hours each day on successive days until desired or conventional bedtime is reached

- 2 AM → 5 AM → 8 AM → 11 AM → 2 PM → 5 PM → 8 PM → 11 PM

Chronotherapy

Progressive phase advance
- Gradually advancing bedtimes (by 30-60 minutes) and waking times until desired schedule is attained

- 3 AM → 2 AM → 1 AM → 12 PM → 11 PM
Advanced Sleep Phase Disorder

- “Morning lark”
- Stable shift in the major sleep period to an earlier time relative to desired or conventional bedtimes
- Early bedtime (6-9 pm) and early wake time (2-5 am)

Irregular Sleep Wake Rhythm

- Absence of stable circadian sleep-wake rhythms
  - Day to day variability in sleep and wake times
- “Atrial fibrillation” of circadian rhythms
  - Irregularly irregular rhythm
- Aggregate sleep time over a 24-hour period is typically normal

Moore R et al. Sleep: A comprehensive handbook, Wiley 2006
Free Running Disorder

- Progressive delay in sleep schedules by about 1 hour or more each day
  - Major sleep period “marches” throughout the 24-hour day
- Periodically recurring complaints of insomnia or excessive sleepiness

Jet Lag

- Westward travel - phase-advanced relative to new time zone
  - Early evening sleepiness and early morning insomnia
- Eastward travel - phase-delayed relative to new time zone
  - Sleep-onset insomnia and morning sleepiness

Shift Work Disorder

- Disparity in timing of sleep-waking due to requirements of work (nighttime) and circadian and homeostatic pressures for sleep (daytime)
- Conventional time cues of sunlight and social activities are frequently out-of-phase with the altered sleep time
Consequences

- Poor work performance
- More sleepiness-related accidents
- Greater absenteeism
- Ischemic heart disease
- Glucose intolerance
- Depression, alcohol and substance dependency

Drake CL. Sleep

Epidemiology

- About 20% of the U.S. workforce is involved in some form of non-standard work schedule
  - Night work (permanent or intermittent)
  - Rotating schedules
  - Early morning work
  - Random work assignments
Epidemiology

- Prevalence of SWSD - 10%
  - Currently working rotating or night schedules
  - Either insomnia or EDS

Drake CL. Sleep 2004

Shift Work Disorder

- Variable individual phase tolerance
- Factors influencing shift work tolerance
  - Age
  - Gender
  - Diurnal preference (“eveningness” vs. “morningness”)
  - Comorbid sleep disorders
Age

- Aging decreased ability to recover after several nights of shift work
- Younger subjects had less sleepiness and were more able to delay their circadian phase

Harma MI. Occup Environ Med 1994

Gender

- Two groups of men or women crane operators from a Polish steel plant
  - Men slept more than women
  - Women had more sleep disturbances and were sleepier during work
  - Women had lower ratings of subjective health

Oginska H. Ergonomics 1993
Gender

- General health among women improved after 4th to 5th decade
- Men had progressive deterioration of health with aging
- Women quit their shift work less often than men

Oginska H. Ergonomics 1993

Phase Preference

- Morning tendency group
  - Sleepier during night shift hours (12:30 am to 4:30 am)
- No difference between groups in total daytime sleep (actigraphy)

Hilliker NA. Sleep 1992
Direction of Shift Change

- Change in shift schedule
  - From a slow backward rotating (E ⇒ M ⇒ N)
  - To a fast forward rotating system (M ⇒ E ⇒ N)
    - Less subjective sleep problems
    - Greater alertness

Hakola T. J Hum Ergol 2001

Countermeasures

- Exposure to bright lights in the workplace
- Scheduled napping
- Administration of wake-promoting agents during evening work hours
- Use of hypnotic agents to improve daytime sleep
Limited Efficacy

- Behavioral countermeasures
  - Increasing levels of activity
  - Changes in posture
  - External stimulation (loud noises)

Light Therapy

- Proper timing, intensity and duration of light treatment has yet to be determined
- Studies have used different treatment schedules
  - Four 20-minute periods during night duty
  - Half of a 12-hr night shift
  - 6 hours of intermittent light exposure
  - 20 minutes during break from work
Light Therapy

- Studies have used various light intensities from 2350 to 12,000 lux
- Some studies have also restricted daytime light exposure

Light Therapy

- Effects of light exposure during night work
  - Improve work performance
  - Decrease sleepiness and tiredness
  - Improve day sleep patterns
  - Improve mood
Yoon IY. Sleep 2002
Scheduled Sleep Periods

- Prescribed napping before, or during, night work
  - Decreases sleepiness
  - Increased alertness
  - Improved reaction times

*Sallinen M. J Sleep Res 1998*
Wake-Promoting Agents

- Wake-promoting agents
  - Caffeine
  - Amphetamine
  - Modafinil / Armodafinil
- Benefits when given during night shift work
  - Improve alertness
  - Decrease sleepiness
  - Enhance performance

Sallinen M. J Sleep Res 1998
Figure 2—Mean maintenance of wakefulness (AWT) in minutes (±SEM bars) for the matched (solid line) and placebo (dashed line) groups at each time point during 4 ultrasound nights. Statistical results are presented in text.

Walsh JK. Sleep 2004

Figure 3—Mean number of lapses (±SEM bars) in the Psychomotor Vigilance Test (PVT) for matched (solid line) and placebo (dashed line) groups at each time point during 4 ultrasound nights. Statistical results are presented in text.

Walsh JK. Sleep 2004
Wake-Promoting Agents

- Should *not* be used chronically to replace obtaining sufficient duration of sleep

Improving Daytime Sleep

- Hypnotic medications can improve daytime sleep quality and duration
  - Benzodiazepines (triazolam)
  - NBBRAs (zopiclone)
  - Melatonin receptor agonists (ramelteon)
- Effect on nighttime alertness and psychomotor performance is inconsistent
Therapy of CRSDs

- Phototherapy – DSPS, ASPS, FRD (light perception), ISWR, JL, SWD
- Melatonin – DSPS, FRD, ISWR, JL
- Planned napping – SWD
- Stimulants and hypnotics – JL, SWD
Conclusion

- Biological rhythms are a fundamental characteristic of life
- Circadian rhythms are genetically controlled
- Circadian rhythms and homeostatic sleep pressure interact to regulate the timing and consolidation of sleep and wake
- Misalignment in the circadian sleep-wake rhythm leads to sleep disturbance