May, 14 2015

Laboratory of Comparative Somnology and Neuroendocrinology, Institute of Evolutionary Physiology and Biochemistry, Russian Academy of Sciences

Circadian Rhythms: Implications for Metabolic and Brain Health

Phyllis C. Zee, MD, PhD
Benjamin and Virginia T. Boshes Professor in Neurology
Director Center for Sleep and Circadian Medicine
Northwestern University Feinberg School of Medicine
Center for Circadian and Sleep Medicine

Ramadevi Gourineni, MD
Brandon Lu, MD*
Kathryn Reid, PhD
Lisa Wolfe, MD
Aleks Videnovich, MD*
Roneil Malkani, MD
Kelly Glaser-Baron, PhD*
Sabra Abbott, MD, PhD
Rodolfo Soca, MD
Seong J Kim, MD
Euyeon Joo, MD
Ivy Cheung
Giovanni Santostasi, PhD
Hryar Attarian, MD

Collaborators:
Fred W. Turek, PhD
Joseph Bass, MD
Ravi Allada, MD, PhD
Eve Van Cauter, PhD
Kristen Knutsom, PhD
Ken Paller, PhD
Marsel Mesulam, MD
Sandra Weintraub, MD
Tanya Simuni, MD
Teepu Siddique, MD
Kiang Liu, PhD
Joseph Kang, PhD
Frank Penedo, PhD

P01 AG11412  R01 HL105549  R01 HL098297
R01 HL092140  U10HD063036  UM1HL112856
U01HL111478  *K23 HL091508  * K23NS072283
*5K12HD05588  NCRR-00048  T32 HL07909
As the world turns…there are prominent dynamic changes in our biology
Circadian Rhythms
Daily Physiologic and Behavioral Patterns

24:00 Midnight
Midnight

22:30
Bowel movements suppressed

21:00
Melatonin secretion starts

19:00
Highest body temperature

18:30
Highest BP

18:00
Greatest cardiovascular efficiency and muscle strength

17:00
Fastest reaction time

15:30
Best coordination

14:30

Noon
12:00

06:45
Sharpest rise in BP

07:30
Melatonin secretion stops

08:30
Bowel movement likely

09:00
Highest testosterone secretion

09:00
High alertness

10:00

18:30
Highest BP

17:00
Greatest cardiovascular efficiency and muscle strength

15:30
Fastest reaction time

14:30
Best coordination

12:00
Noon

02:00
Deepest sleep

04:30
Lowest body temperature

06:00
SLEEP/Wake

06:45
Sharpest rise in BP

07:30
Melatonin secretion stops

08:30
Bowel movement likely

09:00
Highest testosterone secretion

09:00
High alertness

10:00

12:00
Noon

02:00
Deepest sleep

04:30
Lowest body temperature

06:00
SLEEP/Wake

06:45
Sharpest rise in BP

07:30
Melatonin secretion stops

08:30
Bowel movement likely

09:00
Highest testosterone secretion

09:00
High alertness

10:00

BP, blood pressure.
Human Circadian Rhythms
Physiological Cycles

- **Alertness**
  - Median Systolic BP, mm Hg
  - Core Body Temperature, °C
  - Melatonin, pmol/L
  - Mood, Relative Change
  - Subjective Alertness, Deviation From Mean
  - Short-term Memory, Deviation From Mean

- **Memory**
  - Core Body Temperature, °C
  - Mood, Relative Change
  - Short-term Memory, Deviation From Mean

- **Physiological Cycles**
  - Alertness
  - Short-term Memory
  - Core Body Temperature
  - Mood
  - Insulin
  - Leptin

- **References**
  - Scheer, Blood, 2014
Rhythmic expression of clock genes has been found in many tissues and (10%-20%) of all genes are rhythmic)

Marcheva et al, 2013
Gene expression changes across time of day

These modules have different times of peak gene expression.

Courtesy: Ravi Allada, A. Hutchinson
15% of Genes and Metabolites are Rhythmic

(Dallmann, PNAS 2012)
Determinants of Circadian Rhythms and Sleep/Wake Timing

GI, gastrointestinal; PG, pineal gland; RHT, retinohypothalamic tract; SCN, suprachiasmatic nucleus; WBC, white blood cell.

Circadian and Sleep Health Implications for Health and Disease

CRSD, circadian rhythm sleep disorder.
From Clocks to Disease: Rapid Evolution of Circadian Clock Field

National Institute of Mental Health (2008)
National Institutes of Neurological Disorders and Stroke
National Heart, Lung and Blood Institute
National Institute of Diabetes and Digestive and Kidney Diseases
National Institute on Aging
National Institute on Alcohol Abuse and Alcoholism
National Institute of Arthritis and Musculoskeletal and Skin Diseases
National Cancer Institute
Eunice Shriver National Institutes of Child and Health Development
More.........
Circadian Timing, Metabolism, Cardiovascular Function and Risk for Obesity in Humans

Circadian misalignment is associated with adverse effects on appetite, glucose metabolism, cardiovascular function.
Consequences of circadian misalignment on metabolic, autonomic, and endocrine function

Role of Sleep Timing, Food Timing and Light Exposure on Weight and Metabolism

Kathryn Reid, PhD, Kelly Glaser-Baron, PhD, Ivy Cheung
Cumulative Calorie Intake: Late Sleepers (midpoint after 5 AM)

Baron KG et al, Obesity, 2011
Food Intake and Sleep Timing

**Calories after 8 pm**

- **p < .0001**

**Fast foods per week**

**Fruits and vegetables serving per day**
Circadian Timing and Fasting Glucose

**Graph:**
- X-axis: DLMO (clock time) from 18:00 to 0:00
- Y-axis: Fasting Glucose (mg/dl) from 70 to 100
- Scatter plot with a line of best fit
- Correlation coefficient: \( \rho = 0.45, p = 0.045, n = 20 \)

**Text:**

NIDDK R01 (PI Knutson): Preliminary Data
Chronotype & Glycemic Control in Type 2 Diabetes

P=.001 after adjusting for age, sex, race, BMI, insulin use, depressed mood, diabetes complications, and perceived sleep debt.

Reutrakul et al, Diabetes Care 2013
Too much, too little at the wrong time.. Light Exposure Contribution to Obesity?

250,000 years: Fire
5,000 years: Candles
250 years: Gas lighting
120 years: Electric lighting

LIGHT POLLUTION

Ciszaro, Fasti, Elvidge, United Nations Special Environmental Symposium, Vienna (12-16 Luglio 1996)
Timing of Mean Light Exposure and BMI

Every hour later of MLiT above 500 lux = 1.28 BMI

Reid, Santostasi, et al, PLOS One 2014
Effect of Light on Hunger and Metabolism

Yellow shading indicates light exposure; M denotes meal; * p<.05, † p≤0.10
N=14 per group
Regulating light exposure, timing of food intake: Novel approaches to weight Regulation in humans?
Circadian and sleep/wake cycle disturbances are consequence of neurodegeneration.

Circadian and sleep/wake disruption exacerbate symptoms of neurodegeneration.

Improving circadian rhythms and sleep are primarily symptomatic treatments.
Neurodegeneration and Altered Daily Rhythms

Alzheimer’s
Parkinson’s
Huntington’s
Traumatic Brain Injury
Chronic Traumatic Encephalopathy

Delayed/damped rhythms
activity, sleep
temperature
melatonin, cortisol
circadian/clock genes

Neurodegeneration
Circadian/Sleep
Cognition

References
Schlosser Covell et al. 2012
Aziz et al. 2009
Boone et al. 2012
Mathias, Alvaro 2012
Emerging Evidence

Lim and Allada, Science 2013

Ataxin 2 (SCA and ALS) activates translation of PER and alters sleep/wake rhythm
Changes in Cycling Gene Networks as a Basis for Neurodegenerative Diseases

Network A produces damage

Network B protects against damage

Gene Network A
Gene Network B

Time

Age
Injury

Chronotherapeutic

Temporally Targeted Therapy

Daily Neurodamaging Temporal Window
Updated View

Clocks
Sleep/Wake

Neural function

Neuropsychiatric disorders Neurodegeneration

Circadian and sleep function essential for neural function, connectivity and plasticity

Circadian and sleep disruption contribute to brain disorders (psychiatric, neurodegenerative, neurodevelopmental)

Improving circadian rhythms and sleep as targets for prevention and disease modification.
Evidence for sleep-wake and circadian dysfunction in Non-Motor Manifestations of Parkinson’s Disease

Nocturnal sleep disturbances in PD
60% of patients versus 30% of healthy controls

Excessive daytime somnolence (EDS)
16% of patients versus 1% of healthy controls
EDS has been associated with three-fold increase in the risk of developing PD

1Tandberg et al. 1998; 2Abbott et al. 2005
Disturbed sleep - wake cycle in PD - Pathophysiology -

- Motor symptoms of PD
- Complex medication regimens
- Co-existent sleep disorders (sleep apnea, RLS)
- **Primary neurodegeneration of PD**
  - Central sleep regulation centers
    - Locus coeruleus
    - Raphe nucleus
    - PPT nucleus
    - Hypothalamus (hypocretin 1)
  - **Circadian system?**
Circadian dysfunction in a mouse model of Parkinson's disease

Takashi Kudo, Dawn H. Loh, Danny Truong, Yingfei Wu, Christopher S. Colwell *

Department of Psychiatry & Biobehavioral Sciences, University of California-Los Angeles, Los Angeles, CA 90024, USA

Alpha sinuclein overexpression Model of Parkinson’s Disease

Dampened circadian rhythm of Rest-activity of sleep/wake cycle
Rest-Activity Rhythm Characteristics
Parkinson’s Disease

Delayed

Irregular/fragmented

JAMA Neurology, 2014
Circadian Rhythm in PD
Aleks Videnovich K-23 Awardee (NINDS)

PD=20; control 20
Baseline period – 14 days
Actigraphy
Sleep diaries

Duration: 10.3 ± 8.7
UPDRS: 34.3 ± 10.1

Modified Constant Routine Protocol
Clinical Research Unit (3 days/night)

Screening
PSG
8 hours

MSLT
PSG
8 hours

Modified Constant Routine
24 hours

Day 1
Day 2
Day 3
Day 4

Blood sampling every 30 minutes
Circadian Clock Gene Expression in PMBC

control

PD

Preliminary Unpublished
Circadian Rhythm of Melatonin in PD

Videnovich A et al, JAMA Neurology, 2014
Circadian Based Treatments for Sleep Wake Cycle Disorder in Neuropsychiatric Disorders

- Light
- SCN (~24 hour)
- Non-Photic Zeitgebers
  - Timed Melatonin
  - Timed Physical activity
- Hormones
- Other Brain Regions
- Autonomic

Physiology, Mood and Behavior

~24 hour
Light exposure and PD

- Connections between the visual system and DA systems can increase activity on exposure to bright light.  
  \(^1,^2,^3\)

- Improvements in motor performance observed in experimental animals by housing them in a constant ambient light.  
  \(^4\)

- Administration of bright light to patients with PD improves bradykinesia, rigidity and depression scores.  
  \(^5,^6,^7\)

- Most effective frequencies of light are most likely in the blue/green spectrum (500 nm), the frequencies affected in the visual deficits in the PD population.  
  \(^8\)

\(^1\) Iversen 1978  \(^2\) Isaac 1971  \(^3\) Seegal 1971  
\(^4\) Willis 1999  \(^5\) Artemenko 1996  
\(^6\) Willis 2007  \(^7\) Paus 2007  
\(^8\) Adachi-Usami 1990
Bright white Light Exposure Improves Wakefulness in Parkinson’s Disease

- Bright: 3000 lux (N=15)
- Dim Red: 300 lux (N=15)
- 0900-1100; 1700-1900 for 4 weeks

<table>
<thead>
<tr>
<th>Δ EES score</th>
<th>Bright Light</th>
<th>Dim Red Light</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.75 ± 1.84</td>
<td>1.79 ± 2.89</td>
<td>0.002</td>
<td></td>
</tr>
</tbody>
</table>
Light as Novel Therapy for Excessive Sleepiness in PD

• Supplemental exposure to bright light is well tolerated in the PD population.

• Supplemental exposure to bright light is associated with improvements in excessive daytime sleepiness associated with PD.

• Further studies are needed to optimize the wavelength, duration and exposure parameters of light therapy in the PD population.
Northwestern Biochronicity Program

Manipulation of Timing

Cycling gene and Physiology Network Modules

Cardio-metabolic Neuropsychiatric

Therapeutic Targets

(Allada, Turek and Zee)
Integrating the Time Domain into Population Health and Personalized Medicine

- Circadian/rhythmic Biomarkers
  - Sleep/wake
  - Light/Dark
  - Social
  - Work
  - Mood
  - Feeding pattern

- Meal Timing
- Exercise timing

- Metabolic rhythms
- Neuronal activity, motor, cognitive
- Cell cycle, apoptosis and DNA repair
- Oxidative stress
- Metabolism
- Toxin removal
- Angiogenesis

Peripheral organs and tissues

Clinics

Autonomic system

chronotherapeutics
Meeting in the Laboratory of Comparative Somnology and Neuroendocrinology, Institute of Evolutionary Physiology and Biochemistry, Russian Academy of Sciences

Supported by

Dynasty Foundation