Circadian Rhythms in Health and Disease

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Hierarchical organization of the mammalian clock

Panda et al. Science, 2002
Panda et al. Cell, 2002
Panda et al. Science, 2003
Sato et al, Neuron, 2004
Rudic et al. PIOS Biol, 2004
Panda et al. Science, 2005
Miller et al, PNAS, 2007
Hughes et al. PIOS Biol, 2009
Lamia et al. Science 2009
Vollmers et al. PNAS 2009
DiTacchio et al, Science 2011
Cho et al. Nature 2012
Vollmers et al. Cell Metab. 2012
Humans evolved with a clock to adapt to daily natural rhythms in light and food availability.

In post-industrial societies humans will continue living in a clock-disruptive anthropogenic world that has continuous twilight illumination and constant access to food.

A HEALTHY CLOCK

- Sleep
- Alertness/Cognitive ability
- Muscle reaction time
- Pancreas release of insulin & glucagon
- Liver function
- Blood pressure
- Cardiovascular ability & muscle strength

Improved sleep quality, mood, metabolism, cardiovascular health. Decreased risk for disease.

A DISRUPTED CLOCK

- Poor sleep quality
- Depression/mental health
- Hypertension
- Fatty liver disease
- Insulin resistance or type 2 diabetes
- Cardiovascular diseases

Behavior to improve circadian health & promote healthy aging
- Time-Restricted feeding
- Healthy Light exposure
- Regular and sufficient sleep

Behavior that decreases circadian health & demotes healthy aging
- Shiftwork
- Jet lag
- Aging
- Erratic Lifestyle

Decreased sleep quality, mood, metabolism, cardiovascular health. Increased risk for disease.
Circadian clocks: Not your grandfather’s clock

Paul W. Turek

The last 20 years have seen the rapid evolution of our understanding of the molecular genes and networks that enable all forms of life to generate 24-hour/circadian rhythms. One finding that has been particularly striking is the recognition that the circadian clock regulates the timing of many cellular and signaling pathways associated with multiple disease states. Such advances represent a new frontier for medicine, circadian medicine.

REVIEW

Mechanisms linking circadian clocks, sleep, and neurodegeneration

Roderick A. Dunlap and David W. Holterman

Dysfunctions of normal circadian rhythms and sleep cycles are consequences of aging and are profoundly affect health. Accumulating evidence indicates that circadian and sleep disruptions, which have long been considered precursors of many age-related degenerative conditions, may actually drive pathogenesis only in the course of these diseases. In this review, we explore potential critical and molecular mechanisms linking circadian rhythms and sleep with neurodegeneration and Alzheimer’s disease.

REVIEW

Circadian physiology of metabolism

Santit Pasuni CONS

A majority of mammalian genes exhibit daily fluctuations in expression levels, making circadian expression rhythms the largest known regulatory network in normal physiology. Cell-autonomous circadian clocks interact with daily light-dark and feeding-fasting cycles to generate approximately 24-hour oscillations in the function of thousands of genes. Circadian clocks coordinate these circadian oscillations with information derived from the central nervous system. Such inter- and intracellular daily rhythms optimize physiology both by harnessing energy use and by temporally regulating incompatible processes. Experimentally altered models and epidemiological data indicate that chronic circadian rhythm disturbance increases the risk of metabolic diseases. Conversely, time-restricted feeding, which mimics daily cycles of feeding and fasting without caloric restriction, sustains robust daily rhythms and can alterate metabolic parameters. These findings provide new insights into the role of the circadian clock in health and disease and offer a new perspective for treating chronic diseases in which metabolic disturbance is a hallmark.

Immunity around the clock

Andrew Leuck

Immunity is a high-need, high-benefit trait that defends against pathogens and makes the body fat-free, but whose immunopathology can result in immunopathology and sometimes even death. Because many immune parameters oscillate rhythmically with the time of day, circadian clock has emerged as an important regulator for releasing immunity-associated costs, which, in turn, estimates cost, and fitness. This is mediated by the interplay between the daily or seasonal environmental cues and the intrinsic oscillators of immune cells, which help optimize immune responses throughout the circadian cycle. The elucidation of these clock-controlled immunomodulatory mechanisms might uncover new approaches for treating infections and create new avenues for research.

Circadian time signatures of fitness and disease

Joseph Blevins and Mitchell A. Lazar

Immune cells are autonomous circadian oscillators that play a critical role in the acquisition and maintenance of homeostasis. Circadian clocks in immune cells have major impact on fundamental mechanisms through which chronically activated immune themes, such as those involved in circadian rhythms. Here, we provide advances in understanding how regulatory networks are altered in circadian clocks and provide new insights into the circadian effects on physiology.
TRF is preventative and therapeutic

A. Body Weight

B. Body Composition

Chaix et al. Cell metabolism 2014

Girish Melkani
SDSU

Gill et al. Science, 2015
Drosophila Heart: Structure & Function

- Video imaging (3rd segment)
- Conical chamber

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Formula</th>
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<tbody>
<tr>
<td>Diastolic diameter (DD)</td>
<td></td>
</tr>
<tr>
<td>Systolic diameter (SD)</td>
<td></td>
</tr>
<tr>
<td>Diastolic interval (DI)</td>
<td></td>
</tr>
<tr>
<td>Systolic interval (SI)</td>
<td></td>
</tr>
<tr>
<td>Heart period (HP)</td>
<td></td>
</tr>
<tr>
<td>Radial contractility</td>
<td></td>
</tr>
<tr>
<td>Fractional shortening (FS)</td>
<td>$\frac{(DD-SD)}{DD}$</td>
</tr>
<tr>
<td>Heartbeat arrhythmicity</td>
<td></td>
</tr>
<tr>
<td>Arrhythmia index (AI)</td>
<td>$\frac{\text{Standard deviation of HP}}{\text{median HP}}$</td>
</tr>
</tbody>
</table>

Gill et al. Science, 2015
ALF

TRF

3 Wk

5 Wk

Gill et al. Science, 2015

Hatori et al. Cell Metab. 2012
Chaix et al, Cell Metab. 2014
Gill et al. Science, 2015
Arble et al. Obesity, 2009
Sherman et al, FASEB J, 2012
Marinac et al. Cancer epid., 2015
Marinac et al. PLoS ONE 2015
Marinac et al JAMA Oncol, 2016
Chung et al. Metabolism, 2016
Translation: While methods and parameters to monitor and modify nutrition intake is extensively studied, method to monitor and intervene eating pattern in humans needs innovation.

Smartphone-app to monitor and intervene eating pattern

Developed by a Biology graduate student in the lab who trained himself to write iOS app codes and implemented the app in 3 months. Data was stored in a secure server in Salk Inst.
N=156 (65Males/91females), San Diego residents, No shiftworker, No students/employee or relatives of students/employees working at Salk. Average Age = 27.6y, Average BMI=24.74 Kg.Cm⁻²

- Make data logging as simple and as few clicks as possible.
- The best logging is passive collection.
- Transfer the burden of data annotation from users to the researcher.
- Tinker with automatic error estimation.

Average eating or drinking lasts for ~14min. So all “events” recorded within 15min of another event is grouped into one “meal”.

Reminder push notifications 1/day: “Did you eat or drink anything in the past 30min?” “Yes/No”. Fraction of times when the subject answered “Yes” but there was no entry in 30min prior to the answer, is considered false negative rate; 10.34%.
Total events: 26676  
2.1% text entries, 97.9% pictures  
22% (5846) water,  
28% (7420) pre-packaged items with readily accessible nutrition information  
50% (13410) were mixed meals with multiple items.  
Average daily caloric intake  
1947 Kcal; 95% CI: 1917-1977 (mean 1.233 fold over MC; 95% CI: 1.214-1.251)  
(10.34% false reporting rate) 

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects (n)</td>
<td>65</td>
<td>91</td>
<td>156</td>
</tr>
<tr>
<td>Age; years</td>
<td>26.4 (24.8-28.1)</td>
<td>28.4 (26.7-30.2)</td>
<td>27.6 (26.4-28.8)</td>
</tr>
<tr>
<td>Height; cm</td>
<td>177.1 (174.9-179.2)</td>
<td>163.5 (161.9-165)</td>
<td>169.1 (167.5-170.8)</td>
</tr>
<tr>
<td>Initial BMI</td>
<td>25.9 (24.69-27.11)</td>
<td>23.9 (22.86-24.95)</td>
<td>24.74 (23.94-25.53)</td>
</tr>
<tr>
<td>Final BMI (after 3 weeks)</td>
<td>25.82 (24.6-27.04)</td>
<td>23.87 (22.81-24.92)</td>
<td>24.68 (23.88-25.49)</td>
</tr>
<tr>
<td>Change in BMI (after 3 weeks)</td>
<td>-0.08</td>
<td>-0.04</td>
<td>-0.06</td>
</tr>
<tr>
<td>Paired t-test P-value</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
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Feedogram (raster plot of eating events)

Gill and Panda, Cell Metab. 2015
**Challenges:** No off-the-shelf solution to collect, organize, analyze and report daily pattern of food intake. We even don’t know which types of infographics will inform and engage users. All these graphs were generated in Mathematica or Matlab.
When people eat?  How many times we eat?
Interval between meals

Eating Duration

But early breakfast does not correlate with shorter eating duration, as it for >15h
Weekend Metabolic Jetlag

Time of 1st caloric intake

- 40% delayed breakfast by ≥1 h
- 25% delayed breakfast by > 2.1h
- only 7% advanced breakfast by >1h

Time of last caloric intake

- 15% delayed last bite by ≥1 h
- 17% advanced last bite by >1h

% of Daily calories consumed by time X

- <25% food is consumed between 4am-noon
- >1/3rd calories consumed after 6pm

More (>25%) consumed between 6-9pm than between 4am-noon (<25%)
We continue eating as long as we are awake.
Eating pattern in Anthropogenic world

Duration of eating: 50% eat for 15 h or longer
Weekend jet lag: 47% delay or advance breakfast by >1h in weekends
Eating Frequency: 25% food are eaten within 1.5 h of previous meal
<25% food is consumed before noon.
>36% of food is consumed after 6pm.
~100% of maintenance calories is consumed within a 12 h period.

Does BMI correlate with Eating Duration?

BMI does not show a simple correlation with eating duration

Many factors are known to contribute to a person’s BMI: Genetics, Epigenetics, Nutrient quantity, physical activity, etc.

We wanted to test in a subset of individuals that have BOTH >25 BMI and >14h eating duration, whether reduction in eating duration to 10 h without any overt suggestions on activity, or nutrition can reduce body weight.
Time Restricted Feeding (TRF) supports sustained weight loss and improvement in subjective quality of sleep.
Summary

A feasibility pilot study that shows individuals can restrict their eating duration to a self selected 10-12 h in natural living condition for several weeks.

TRF reduced body weight among a moderately overweight cohort by 3.8% that was sustained for a year.

However, Time restriction also led to reduced daily caloric intake by ~20%. So the study remains inconclusive whether TRF without reducing calories is beneficial. This may be tested in a controlled laboratory study.

If TR leads to CR, this method may be used to support caloric reduction among target at-risk population.

Age, ethnicity, and BMI associated changes in eating pattern
Eating Pattern in urban India.
75 subjects were given cheap phones to take pictures of all ingestion events.
The Next App (and digital ecosystem)

* myCircadianClock App Functionality:
  - Functions in both Android and iOS devices
  - Tabs to log food, sleep, and activity.
  - Tabs to log weight and vital signs
  - Ability to share Google Fit and Apple HealthKit data
  - Data summary and charts in app (can be activated under specific criteria)
  - Customizable surveys, reminders, prompts, push notifications
  - In App feedback and questions to the study coordinator
  - Online consent and app activation through activation code
  - Runs on a secure cloud server
  - Backend can be customized to run multiple studies under single coordinator and sharing between approved collaborators
  - Daily summary to study coordinator.

* myCircadianClock.org website function
  - Basic information about the app
  - Informed consent
  - Blogs
  - Science
  - Information videos
  - App FAQ

Development process
  ~12 months, 4 part time programmers (Android, iOS, database, website, security, testing)

Emily Manoogian
Open “myCircadianClock.org”

Tell us a little about yourself

If you consent to participate. You will get an activation code in your email

Download the “myCircadianClock” app from App store or Google play

Start using the app to log your food, sleep, and activity