Circadian Biology in Health and Disease

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Northwestern University
Evanston, IL
Rapid Evolution of Circadian Clock Field and its Role in Health and Disease

Basic Research
• Descriptive
• Physiological basis and interaction with multiple systems
• Genetics
• Molecular basis and interactions with multiple molecular and cellular pathways

Health Implications
• Shiftwork/jetlag
• Aging
• Obesity
• Diabetes
• CVD
• Cancer
• Mental disorders
• GI disorders
• Others
Obesity...a circadian/sleep disorder?
Before Present

250,000 years  Fire
5,000 years    Candles
250 years      Gas street lighting
120 years      Electric lighting
Circadian Rhythm of Fatigue During Seventy-two Hours of Sleep Deprivation

(Akerstedt & Froberg, 1977)
Activity Rhythms in Rodents
Flew Mouse from London to Chicago
Properties of Circadian Rhythms

• Self-sustaining, endogenous
• Period ≈ 24 hours
• Synchronized by light-dark cycles
• Master “clock” in the Suprachiasmatic Nuclei (SCN) of the hypothalamus
Discovered in 1972

In Mammals the Clock is Located in the Suprachiasmatic Nucleus
Discovered circa 2000
10–30% of expressed genes are under circadian control.
Early 1990s
No Mammalian Circadian Clock Genes: How to Find Them?

Mutagenesis and Phenotypic (Circadian) Screening Program
C57BL/6J

ENU

C57BL/6JM

10-12 wks

10-12 wks

X

C57BL/6JF

Screen G1 offspring
“That’s fine for fruit flies, but you’d never find such a single gene affecting behavior in a mammal. Mammalian behavior is much more complex.”

—Anonymous comment to Martha Vitaterna
You are on a fishing expedition!

—Anonymous comment to Fred Turek

Response: Yes, but we might catch a big fish.
Discovery of the Mutant

Distribution of period in G1 mice

- Normal C57BL/6
- Putative mutant C57BL/6

Vitaterna et al., 1994
Clock is a semidominant mutation
Clock is a point mutation

Wild-type

Clock/Clock

King et al., Cell 1997
Domino Effect:
Discovery of one gene leads to another

CLOCK  BMAL  CRY  PER  TIM  ?
Liver Has Rhythm
Fred W. Turek and Ravi Allada
Hepatology, April 2002
Genetic Model for Disrupted Circadian Clock
Obesity and Metabolic Syndrome in Circadian Clock Mutant Mice


Science 308, 13 May 2005, p. 1043-1045
Sleep, Circadian and Metabolic Phenotypes of the *Clock* mutant model

Turek et al., 2005
<table>
<thead>
<tr>
<th>Metabolic parameters</th>
<th>WT</th>
<th>Clock</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triglyceride (mg/dl)</td>
<td>136 ± 8</td>
<td>164 ± 8</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Cholesterol (mg/dl)</td>
<td>141 ± 9</td>
<td>163 ± 6</td>
<td>&lt; 0.05</td>
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<tr>
<td>Glucose (mg/dl)</td>
<td>130 ± 5</td>
<td>161 ± 7</td>
<td>&lt; 0.01</td>
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<tr>
<td>Insulin (ng/ml)</td>
<td>1.7 ± 0.3</td>
<td>1.1 ± 0.1</td>
<td>N.S.</td>
</tr>
<tr>
<td>Leptin (ng/ml)</td>
<td>3.4 ± 0.4</td>
<td>4.6 ± 0.3</td>
<td>&lt; 0.05</td>
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</tbody>
</table>

*Turek et al, 2005*
When the *Clock* stops ticking, metabolic syndrome explodes

Lifestyle → GR → PPARα → PPARγ → Rev-erbα → RORα → BMAL1 → CLOCK → Output regulators

Metabolic syndrome
- Visceral obesity
- Insulin resistance
- Dyslipidemia
- Hypertension
- Cardiovascular disease

Nature Medicine
Staels, 2006
And CVD Cancer GI AD Genes
Circadian Dysregulation and Metabolism/Body Weight Regulation

- Genetic Models
- Environmental Models
Circadian Timing of Food Intake Contributes to Weight Gain

Deanna M. Arble¹, Joseph Bass¹, Joseph Bass², Aaron D. Laposky¹, Martha H. Vitaterna¹ and Fred W. Turek¹

Obesity, 2009
“Time of Feeding” Protocol

9wk old B6 males
L : D

Regular Control
Regular
Regular
N = 10

High Fat Control
High Fat
High Fat
N = 10

High Fat Dark
High Fat
N = 6

High Fat Light
High Fat
N = 6

• Measurements:
  – Continuous IR beam break activity
  – Biweekly body weight
  – Weekly food intake
  – Post-mortem body composition
“Wrong” timed feeding leads to increased weight gain

* p < 0.05; post-hoc comparison from Repeated-Measures ANOVA

Arble et al., 2009 Obesity
Out-of-Phase Feeding
Central vs. Peripheral Circadian Rhythm Dyssynchrony
Obesity Trends* Among U.S. Adults

BRFSS, 1985

(*BMI ≥ 30, or ~ 30 lbs overweight for 5’4” woman)

Obesity Trends* Among U.S. Adults

BRFSS, 1990

(*BMI ≥ 30, or ~ 30 lbs overweight for 5’4” woman)

Obesity Trends* Among U.S. Adults
BRFSS, 1995

(*BMI ≥ 30, or ~ 30 lbs overweight for 5’4” woman)

No Data  <10%  10%-14%  15%-19%  20%

Obesity Trends* Among U.S. Adults
BRFSS, 2000

(*BMI ≥ 30, or ~ 30 lbs overweight for 5’4” woman)

Obesity* Trends Among U.S. Adults

Obesity = BMI ≥ 30 (about 30lbs overweight for 5'4'' adult)
After a two-year visit to the United States, Michelangelo’s David is returning to Italy.....
His Proud Sponsors in the U.S.A. were:
Circadian Dysregulation and…

A. National Institute of Mental Health: 2008
B. National Heart, Lung and Blood Institute: 2009
C. National Institute of Diabetes and Digestive and Kidney Diseases: 2010
D. National Institute on Aging: 2010
E. National Institute on Alcohol Abuse and Alcoholism – RFA March 2011 “Circadian Rhythms and Alcohol-Induced Tissue Damage”
F. National Institute of Arthritis and Musculoskeletal and Skin Diseases: April 4, 2013
Effect of weekly reversal of the LD cycle on locomotor behavior

Penev et al. 1998. *Am J Physiol*
Effect of weekly reversal of the LD cycle on mortality

Penev et al. 1998. *Am J Physiol*
Changes in bodyweight of Shifted and Non Shifted animals with and without a colitis challenge

![Graph showing bodyweight changes over days for Phase Shifted (DSS), Non Shifted (DSS), Phase Shifted Control, and Non Shifted Control groups.](image)

- **Phase Shifted (DSS)**
- **Non Shifted (DSS)**
- **Phase Shifted Control**
- **Non Shifted Control**
Environmental and genetic circadian rhythm disruption increases gut permeability in response to chronic alcohol.
C57BL/6J Phase Shift Results

Percentage of mice

- No Phase Shift: 11/12
- Phase Delays: 9/18
- Phase Advances: 4/18

* p < 0.05
Sleep duration & obesity in the U.S.

![Graph showing the relationship between sleep duration and obesity prevalence over time (1950-2010). The graph indicates a decrease in sleep duration and an increase in obesity prevalence.]
### Sleep duration and obesity: epidemiologic studies (December 2010)

<table>
<thead>
<tr>
<th></th>
<th>TOTAL # OF STUDIES</th>
<th># OF STUDIES IN CHILDREN</th>
<th># OF STUDIES IN ADULTS</th>
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<tbody>
<tr>
<td></td>
<td>POSITIVE FINDINGS</td>
<td>TOTAL # OF STUDIES</td>
<td>POSITIVE FINDINGS</td>
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<tr>
<td>CROSS-SECTIONAL STUDIES</td>
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<td>49</td>
<td>21</td>
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<tr>
<td>PROSPECTIVE STUDIES</td>
<td>12</td>
<td>13</td>
<td>7</td>
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<tr>
<td>ALL STUDIES</td>
<td>76</td>
<td>84</td>
<td>28</td>
</tr>
</tbody>
</table>
Henry VIII

Royal Road to Obesity
• Great progress in unraveling molecular basis of circadian clock

• Little progress in unraveling molecular basis of sleep regulation
Sleep Genes and Health

Waiting for Blueprint
Circadian Disruption and Human Health

- Shiftwork / Jet lag
- Regulation of sleep-wake cycle
- Brain and Peripheral Tissue Specific – Circadian Gene Dysregulation

NEW FRONTIER

Human Mental & Physical Health at Many Levels
(Obesity, Diabetes, CVD, Depression)
da Vinci: Helicopter Blueprint 1493

Circadian Clock Genes & Health: The Blueprint is there!

500 years to build
A Tipping Point

Circadian Medicine

Circadian Health
Sleep vs. Circadian Clinics in US

• ≈ 6,000 Sleep Clinics
• 0.000 Circadian Clinics

However...
Circadian Clinic

Dr. Phyllis Zee at Northwestern University

Dr. Fred Turek
Dr. Ravi Allada
Grant Support from:

- NIH – NHLBI, NIA, NIAAA, and NICHD
- March of Dimes
- Merck
- Servier
- American Waterways Operators
- Ingram Barge Company
- Transportation Research Board: NRC/NAS
- Department of Defense (DARPA)
- NASA
## Recent and Present Collaborators

### Collaborating Faculty:
- **Ravi Allada**
- **Joseph Bass**
- **Ketema Paul**
- **Lawrence Pinto**
- **Kathy Reid**
- **Kazu Shimomura**
- **Joseph Takahashi**
- **Martha Vitaterna**
- **Phyllis Zee**

### Collaborators from Rush University:
- **Chris Forsyth**
- **Ali Keshavarzian**
- **Robin Voigt**

### Fellows, Students and Staff:
- **Deanna Arble**
- **Karrie Fitzpatrick**
- **Vance Gao**
- **Susan Hall-Perdomo**
- **Peng Jiang**
- **Katie Lind**
- **Jason Long**
- **Kazu Nohara**
- **Christopher Olker**
- **Sue Losee-Olson**
- **Joe Owens**
- **Eun Joo Song**
- **Keith Summa**
- **He (Sarina) Yang**
- **Lili Zhou**
Circadian Medicine: The Next Frontier

The Journey Continues…