Central and Peripheral Circadian Clocks

Session 1: Circadian Rhythms and Digestive Disease: Where we Stand

Fred W. Turek, PhD
Director, Center for Sleep and Circadian Biology
Northwestern University
Evanston, IL
Before Present

250,000 years  Fire

5,000 years  Candles

250 years  Gas street lighting

120 years  Electric lighting
Artificial Night Sky Brightness due to Light Pollution in North America
A preliminary picture of the growth from 1950 to 2025

© 2001 Cinzano P., Falchi, F., Elvidge, C.D.
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?
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: 2013
G. National Institute of Environmental Health Sciences: 2016
Internal clocks are not always in sync with external life.
Sleep in Permanent & Rotating Shift Workers

- **Permanent**
- **Rotator**

<table>
<thead>
<tr>
<th>Shift</th>
<th>Hours of Sleep</th>
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<tbody>
<tr>
<td>Day</td>
<td>7</td>
</tr>
<tr>
<td>Evening</td>
<td>8</td>
</tr>
<tr>
<td>Night</td>
<td>5</td>
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Social Jet Lag

Till Roenneberg
Circadian Dysregulation

• Genetic Models

• Environmental Models
Clock is a semidominant mutation
Domino Effect:
Discovery of one gene leads to another

CLOCK  BMAL  CRY  PER  TIM  ?
Obesity and Metabolic Syndrome in Circadian Clock Mutant Mice


Science 308, 13 May 2005, p. 1043-1045
When the *Clock* stops ticking, metabolic syndrome explodes

Circadian control depends on oscillating transcription factors, master switches synchronized by stimuli such as light and feeding. Recent studies show that altering circadian rhythmicity also results in pathophysiological changes resembling the metabolic syndrome.

THE CLOCKS WITHIN US

Genes in the liver, pancreas and other tissues (not just the brain) keep the various parts of your body in sync. Timing miscues may lead to diabetes, depression and other illnesses

By Keith C. Summa and Fred W. Turek
Clocks are everywhere in our bodies.
Peripheral Clocks

Maury et al., Circ Res 2010
Reppert and Weaver (2002)
Nature (418): 935

Figure 1 The mammalian circadian timing system is a hierarchy of dispersed oscillators. a, The master clock in the SCN is composed of numerous clock cells. The SCN receives light information by a direct retinohypothalamic tract (RHT) to entrain the clock to the 24-h day. The entrained SCN, in turn, coordinates the timing of slave oscillators in other brain areas (for example, cortex) and in peripheral organs (for example, kidney and liver). b, A single SCN neuron in culture expresses robust circadian rhythms in firing rate over 9 days of study, proving that the core clock mechanism is contained within single cells (adapted from ref. 83). SCN and liver explants from transgenic rats expressing a mRl/t-driven luciferase reporter gene exhibit bioluminescence rhythms in culture; the black and white bars along the x-axis indicate the light-dark cycle at the time of tissue collection (adapted from ref. 9). The SCN explant rhythm persists for weeks in culture, whereas the liver explant rhythm dampens. A medium change on day 7 restarts the liver oscillation, showing that the dampening was not due to tissue death.
Circadian Dysregulation

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

Deanna M. Arble¹, Joseph Bass¹,², Aaron D. Laposky¹, Martha H. Vitaterna¹ and Fred W. Turek¹
“Time of Feeding” Protocol

9wk old B6 males

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<tbody>
<tr>
<td>Regular Control</td>
<td>Regular</td>
<td>Regular</td>
<td>10</td>
</tr>
<tr>
<td>High Fat Control</td>
<td>High Fat</td>
<td>High Fat</td>
<td>10</td>
</tr>
<tr>
<td>High Fat Dark</td>
<td>High Fat</td>
<td>High Fat</td>
<td>6</td>
</tr>
<tr>
<td>High Fat Light</td>
<td>High Fat</td>
<td>High Fat</td>
<td>6</td>
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• 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
Sleep and Disease
Importance of Sleep for Obesity, Diabetes and CVD

Eve Van Cauter Group at University of Chicago 1999
**PROTOCOL FOR SLEEP DEBT STUDY**

**BASELINE**
- 8-h bedtime

**SLEEP DEBT**
- 4-h bedtime

**SLEEP RECOVERY**
- 12-h bedtime

**CLOCK TIME**
- 09 13 17 21 01 05 09

**DAY**
- B1
- B2
- B3
- D1
- D2
- D3
- D4
- D5
- D6
- R1
- R2
- R3
- R4
- R5
- R6
- R7

**Influenza vaccination**
IVGTT: Glucose

PLASMA GLUCOSE (mg/dl)

Time After Glucose Infusion (min.)

Van Cauter
IVGTT: Insulin

- Time After Glucose Infusion (min.)
- Plasma Insulin (pmol/L)
- Short Sleepers
- Normal Sleepers
After a two-year visit to the United States, Michelangelo’s David is returning to Italy.....
His Proud Sponsors in the U.S. were:
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

500 years to build

Circadian Clock Genes & Health: The Blueprint is there!
A Tipping Point

Circadian Medicine

Circadian Health
Sleep vs. Circadian Clinics in the U.S.

- ≈ 6,000 Sleep Clinics
- 0.000 Circadian Clinics

However…
0.0001 Circadian Clinic

The Center for Circadian and Sleep Medicine

Dr. Phyllis Zee
Dr. Ravi Allada
Dr. Fred Turek
Recent and Present Collaborators

Collaborating Faculty:

- Ravi Allada
- Joseph Bass
- Ken Paller
- Ketema Paul
- Lawrence Pinto
- Kathy Reid
- Kazu Shimomura
- Joseph Takahashi
- Martha Vitaterna
- Phyllis Zee

Fellows, Students and Staff:

- Samuel Bowers
- Adam Braeckman
- Helen Considine
- Vance Gao
- Susan Hall-Perdomo
- Peng Jiang
- Katie Lind
- Christopher Olker
- Eun Joo Song
- Keith Summa

Collaborators from Rush University:

- Chris Forsyth
- Ali Keshavarzian
- Robin Voigt
• Circadian rhythmicity reigns across the spectrum of human life, from gene transcription in the cell nucleus, to organ function, behaviour and demography.

• How naïve of mankind to think that induction of chaos in this ancient and ubiquitous timing system could come without significant physiological consequence.
Circadian Medicine: The Next Frontier

The Journey Continues…