“The Role of Sleep and Arousal in the Development of Obesity"

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SLEEP
CIRCADIAN RHYTHMS
FUEL METABOLISM
FROM THE BEGINNING
CIRCADIAN CLOCK (SCN)

- Light
- LGN
- Sleep-Wake Cycle
- Eye
- FIHT

Output Rhythms
- Endocrine
- Behavioral
- Metabolic
- Seasonal Rhythms
Suprachiasmatic nucleus (SCN)
“Master Circadian Pacemaker”

• Lesioning the SCN abolishes most biological rhythms
Circadian regulation of sleep

Two-Process model: The circadian pacemaker modulates the time of sleep and wake onset

- C and S are independent processes, that interact to optimize the quantity and quality of sleep.
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)

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

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

(*BMI ≥ 30, or ~ 30 lbs overweight for 5'4" woman)

Obesity Trends* Among U.S. Adults

BRFSS, 2000

(*BMI ≥ 30, or ~ 30 lbs overweight for 5'4" woman)

Average sleep duration of the normal working population has decreased from about 9 hours per night in 1910 to about 7.5 hours currently, a trend that is inverse to that of obesity.
Importance of Sleep for Obesity, Diabetes and CVD

Eve Van Cauter Group at University of Chicago
1999
From Van Cauter
IVGTT: Glucose

PLasma Glucose (mg/dL)

Time After Glucose Infusion (min.)

From Van Cauter
INSULIN SENSITIVITY

$10^4 \text{ min}^{-1} \cdot \mu\text{U}^{-1} \cdot \text{ml}^{-1}$

$p = 0.002$

Short Sleepers

Normal Sleepers

From Van Cauter
Henry VIII
Royal Road to Obesity
Neuroscience of Drug Reward: Relevance to Food Reward

F.J. Vaccarino, PhD
Professor and Chair, Department of Psychology
Professor, Department of Psychiatry
University of Toronto

Principal Editor,
Neuroscience of Psychoactive Substance Use and Dependence
Published by World Health Organization, 2004
• Links between food reward and drug reward: individual differences
• Effects of sleep deprivation on food reward and drug award
• Effects of Stress on food reward and drug reward
• Reward signals, food choices and different macronutrients
• Beyond Dopamine

From Vaccarino
Natural Factors Associated with Enhanced DAergic Transmission

- **Intrinsic:** hunger
  - sex
  - curiosity/exploration

- **Extrinsic:** sweet food
  - attractive sexual stimuli
  - enriched environment

*From Vaccarino*
Sleep deprivation produces behavioral supersensitivity to DA agonists, amphetamine and cannabis in rats

Tufik et al., 1978
Ferguson et al., 1969
Carlini et al., 1977
Table. Average Ratings of Appetite after 2 Days of Sleep Restriction or Sleep Extension

<table>
<thead>
<tr>
<th>Food Category*</th>
<th>Ratings for 10 h in Bed (n = 12)</th>
<th>Ratings for 4 h in Bed (n = 12)</th>
<th>P Value</th>
<th>Change, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sweets (cake, candy, cookies, ice cream, and pastry)</td>
<td>5.4</td>
<td>6.6</td>
<td>0.03</td>
<td>33</td>
</tr>
<tr>
<td>Salty food (chips, salted nuts, pickles, and olives)</td>
<td>5.0</td>
<td>6.7</td>
<td>0.02</td>
<td>45</td>
</tr>
<tr>
<td>Starchy food (bread, pasta, cereal, and potatoes)</td>
<td>5.9</td>
<td>7.4</td>
<td>0.03</td>
<td>33</td>
</tr>
<tr>
<td>Fruits and fruit juices</td>
<td>6.4</td>
<td>7.2</td>
<td>0.07</td>
<td>17</td>
</tr>
<tr>
<td>Vegetables</td>
<td>5.6</td>
<td>6.6</td>
<td>0.02</td>
<td>21</td>
</tr>
<tr>
<td>Meat, poultry, fish, and eggs</td>
<td>5.9</td>
<td>6.9</td>
<td>0.11</td>
<td>21</td>
</tr>
<tr>
<td>Dairy (milk, cheese, and yogurt)</td>
<td>5.5</td>
<td>6.4</td>
<td>&gt;0.2</td>
<td>19</td>
</tr>
<tr>
<td>Overall appetite†</td>
<td>39.7</td>
<td>47.7</td>
<td>0.01</td>
<td>23</td>
</tr>
</tbody>
</table>

* Each category is rated on a 0- to 10-cm visual analogue scale.
† Rated on a 0- to 70-cm visual analogue scale.

Sweets - 33%
Salty foods - 45%
Starchy foods - 33%

Spiegel et al., 2004
Biological Relevance of Reward

- Stimuli with positive affective valence increase reward system activity.
- Increased reward system activity is expressed as increased behavior directed at the relevant stimuli.

From Vaccarino
FOOD and EATING

energy regulation

Hedonics

From Vaccarino
Links Between Food Reward and Drug Reward:

Evidence from Individual Differences in Reward and Dopamine Sensitivity

From Vaccarino
SLEEP

CIRCADIAN RHYTHMS

FUEL METABOLISM

FROM THE BEGINNING
Discovery of the Mutant

Distribution of Period in G1 mice

\[ \bar{x} = 23.7 \]
\[ SE = 0.17 \]
\[ N = 205 \]
Clock is a semidominant mutation
Discovery of Clock Gene Led to Discovery of Many Clock Genes
Liver Has Rhythm
Fred W. Turek and Ravi Allada

Hepatology, April 2002
Core circadian clock genes
Transcriptional – translational feedback loop
**Clock/Clock** mice: Baseline sleep

- **Reduced amplitude of sleep-wake cycle (NREM %)**
- **Increased wake time (+ 2 hrs/day)**

(Naylor et al., 2000)

(Easton, 2004)
Sleep in Bmal1/Mop3 −/− mice

• Increased total sleep time (+ 1.5 hours)

- Increased sleep fragmentation
- Impaired recovery from sleep deprivation

Laposky et al., (2005), SLEEP
<table>
<thead>
<tr>
<th>Circadian clock genes influence total sleep amount, sleep consolidation, and sleep homeostasis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
</tbody>
</table>

- Different sleep phenotypes for different circadian genes
- Phenotypes maintained in L:D and D:D
From Flies to Mice (to Humans)

- Core clock genes influence sleep regulatory processes
- Amount, consolidation, sleep architecture, sleep rebound
Obesity and Metabolic Syndrome in Circadian Clock Mutant Mice


Science 308, 13 May 2005, p. 1043-1045
Increased Body Weight of Clock Mutants

From Science 2005
Sleep, Circadian and Metabolic Phenotypes of the *Clock* mutant model

From Science 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>
</tr>
<tr>
<td>Glucose (mg/dl)</td>
<td>130 ± 5</td>
<td>161 ± 7</td>
<td>&lt; 0.01</td>
</tr>
<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>
</tr>
</tbody>
</table>
Diurnal rhythms in the mediobasal hypothalamus

Wild-type = red

CI/CI mutant = black

Turek et al., Science (2005)
Interactions of Circadian Regulation of Sleep and Feeding

Saper et al., TINS 28:152-157, 2005
When the Clock stops ticking, metabolic syndrome explodes

Bart Staels

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.

Figure 1 Transcriptional control of metabolic pathways by circadian oscillators. The molecular circadian oscillator is composed of two coupled feedback loops—Per-Cry and Clock-Emal1—that regulate each other rhythmically. These feedback loops also control the expression of downstream transcription factors such as DBP, HLF and TEF. The circadian oscillator can be modulated by light, which acts on the suprachiasmatic nucleus (SCN) in the brain, and by metabolic stimuli such as hormones and nutritional status, which act on peripheral tissues. The transcription factors of the Clock machinery also regulate genes involved in metabolic control in peripheral tissues such as liver and adipose tissue.
The *ob/ob* mouse: a genetic animal model for metabolic disorders

1. Obesity arose from spontaneous mutation of leptin gene (*ob*)
2. In addition to obesity, *ob/ob* mice are hyperphagic, and exhibit a metabolic syndrome characterized by:
   - hyperglycemia
   - glucose intolerance
   - hyperinsulinemia
Altered sleep regulation in *ob/ob* mice

- **Increased sleep time** (+ 1 hour/day)
- **Increased sleep fragmentation**

**Total sleep time**

**Stage Shifts**

Laposky et al., (2006), Am J Physiol
Effect of leptin repletion on sleep in \textit{ob/ob} mice

Leptin normalizes NREM sleep time between genotypes

Sleep effects do not correlate with body weight

- **Vehicle**
- Leptin (3 days)
  - 100 ug/kg/day, mini-pump
- Leptin (14 days)
  - 100 ug/kg/day, mini-pump

**NREM sleep time**

**Body weight (leptin, ZT2)**
Sleep in animal models of obesity/diabetes

- *ob/ob* mice (leptin deficient)
- *db/db* mice (leptin resistant)
- diet induced obesity - mice
- Zucker Diabetic Fatty rats
“While there is a growing awareness among some sleep, metabolic, cardiovascular, and diabetes researchers that “insufficient sleep” could be leading to a cascade of disorders, few in the general medical profession or in the lay public have yet made the connection.”

Substitute circadian dysregulation for insufficient Sleep
Effect of weekly reversal of the LD cycle on locomotor behavior

Am. J. Physiol. 275
Penev, et al., 1998
Effect of weekly reversal of the LD cycle on mortality

Am. J. Physiol. 275
Penev, et al., 1998
Chronic Disrupted Sleep/Circadian Rhythms

Three fundamental discoveries in just last few years:

- Chronic sleep loss leads to obesity/diabetes and CVD
- Circadian dysregulation leads to disease and metabolic dysfunction
- Molecular circadian clock core machinery: EVERYWHERE
Circadian clock genes are everywhere!!

Fig. 2. The master clock (SCN) governs the peripheral tissue rhythm in mammals. The fact that the rhythmic expression of RPER2 mRNA in several tissues completely depends on the SCN suggests that some signals (Humoral Factors) are needed to maintain coordinate the rhythm of the whole body.

Ishida, Kaneko and Allada (1999)
PNAS, 96: 8819-8820
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 via a direct retinal/paraventricular (PVN) tract to entrain the clock to the 24-h day. The entrained SCN, in turn, coordinates the timing of slave oscillators in critical 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. 12). SCN and liver explants from transgenic rats expressing a mPer1-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.
Nearly ten percent of genes have a circadian rhythm in their expression.

Panda et al., Cell, 2002
Circadian Disruption and Human Health

Shiftwork/Jet lag

Brain Tissue Specific – Circadian Gene Dysregulation

Regulation of sleep-wake cycle

NEW FRONTIER

Human Mental & Physical Health at Many Levels
Present Collaborators

Collaborating Faculty:

Ravi Allada
JOSEPH BASS
Kazu Shimomura
Joseph Takahashi
Martha Vitaterna
Phyllis Zee
AARON LAPOSKY
Christine Dugovic

Recent/Present/Fellows/Students in Turek Lab:

Youngsoo Kim
Sue Losee-Olson
Ketema Paul
Jonathan Shelton
Felix Nunez
He (Sarina) Yang
Karrie Mrazek
Deanna Arble
Deanna Williams
Joe Owens-Ream
Lili Zhou