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

Dr. Fred W. Turek

Center for Sleep & Circadian Biology

Northwestern University

Treatment and Prevention of Obesity: Approaches and Needs
Copenhagen
September 12, 2007

SLEEP

CIRCADIAN

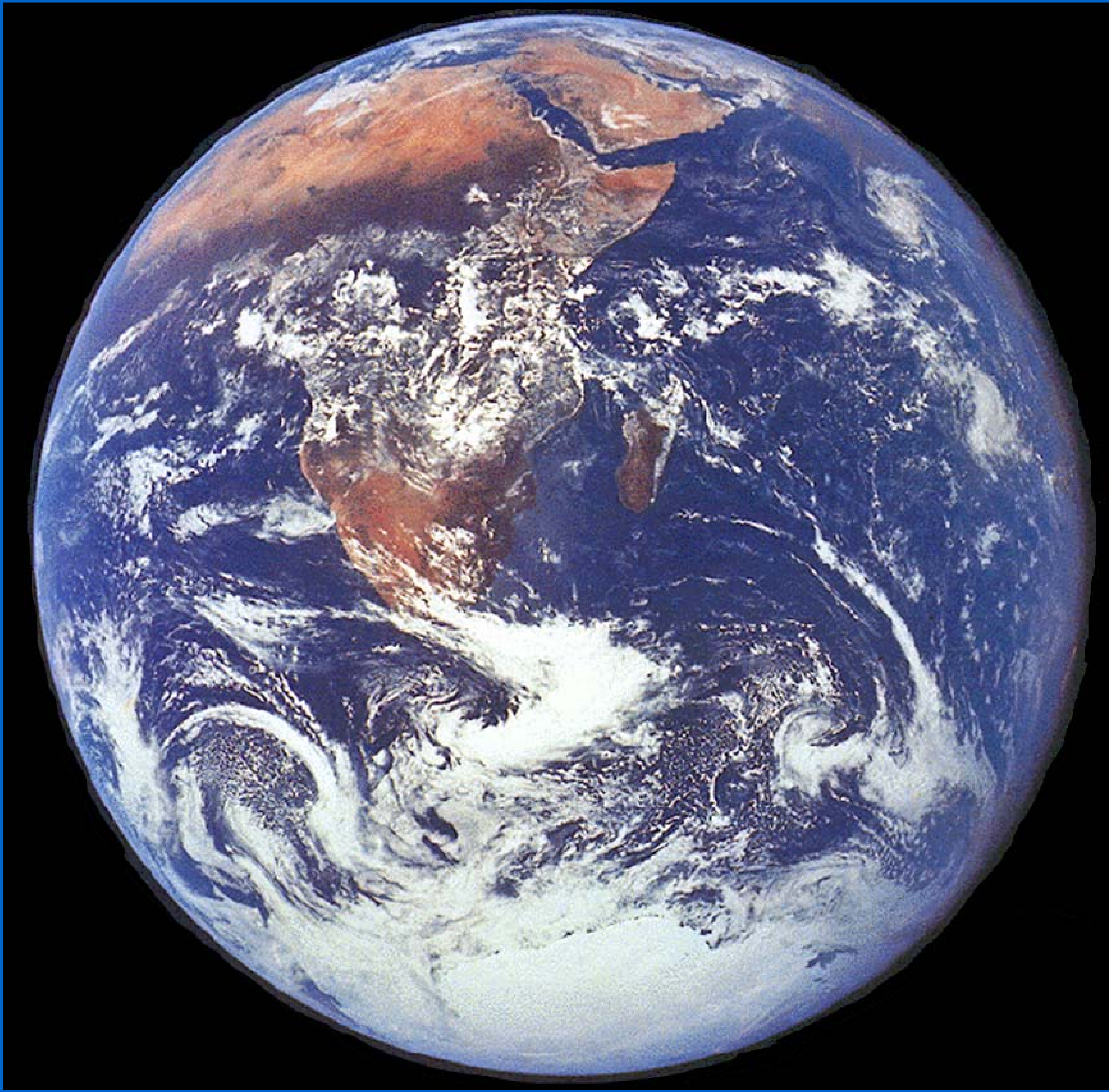
RHYTHMS

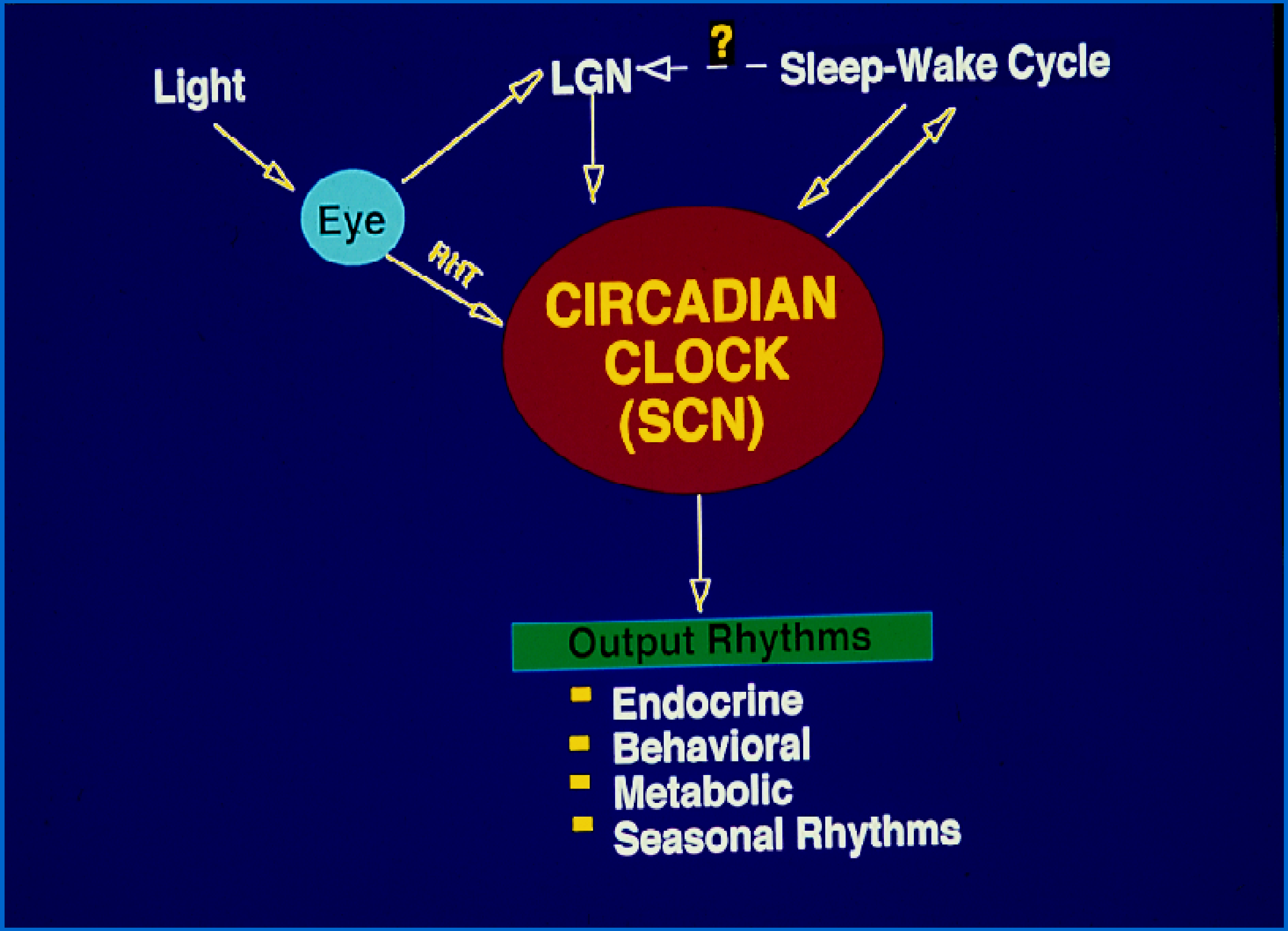
FUEL

METABOLISM

FROM THE

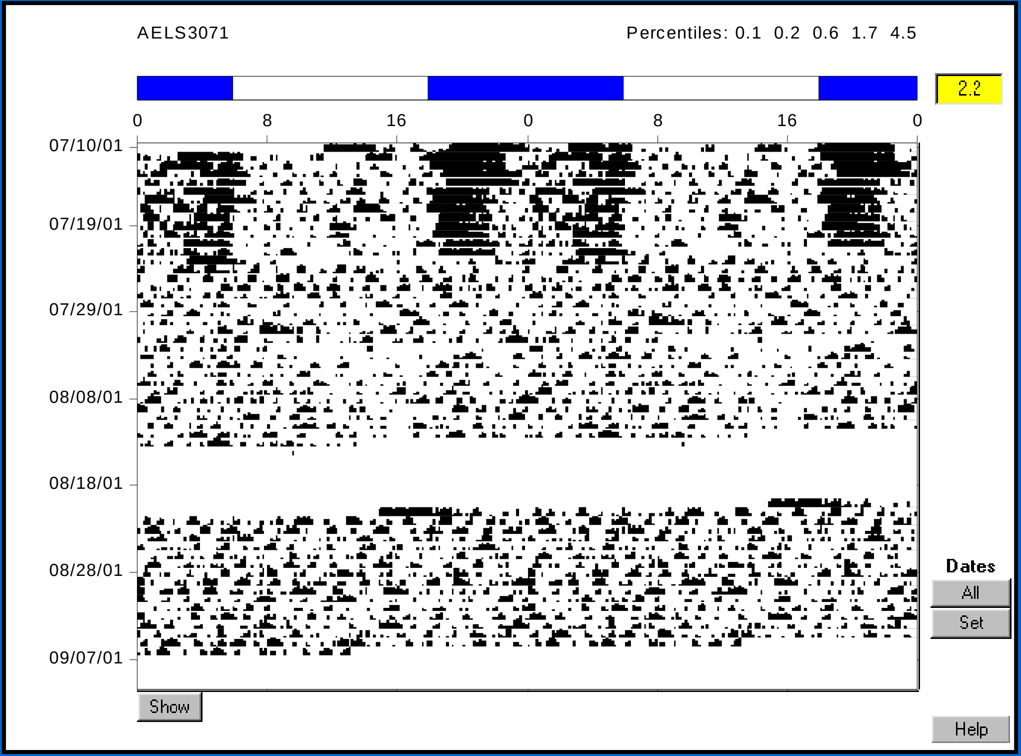
BEGINNING




Light
LGN
?
Sleep-Wake Cycle
Eye
RHT
CIRCADIAN
CLOCK
(SCN)
Output Rhythms
Endocrine
Behavioral
Metabolic
Seasonal Rhythms

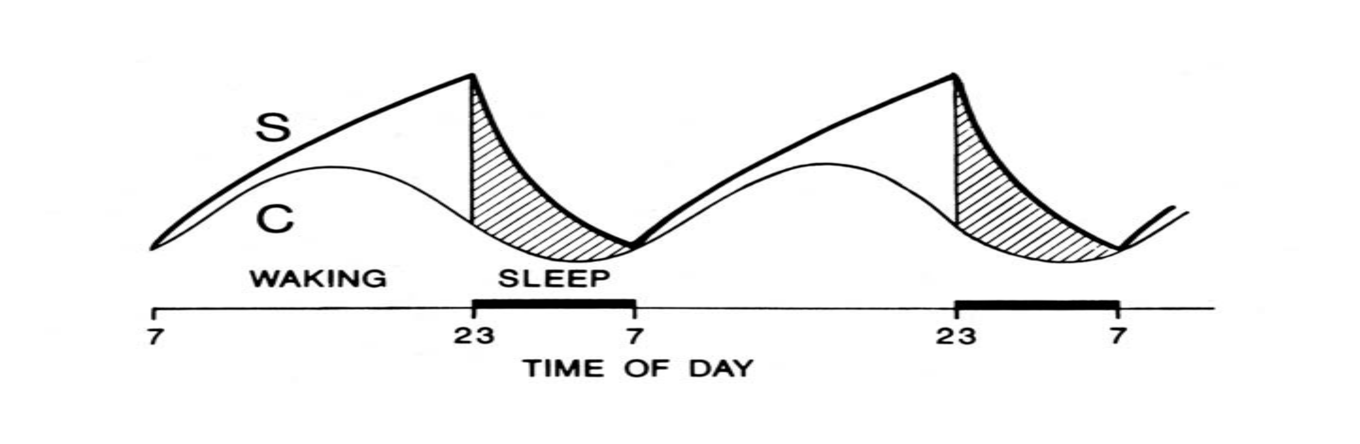
Suprachiasmatic nucleus (SCN)
"Master Circadian Pacemaker"

- **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

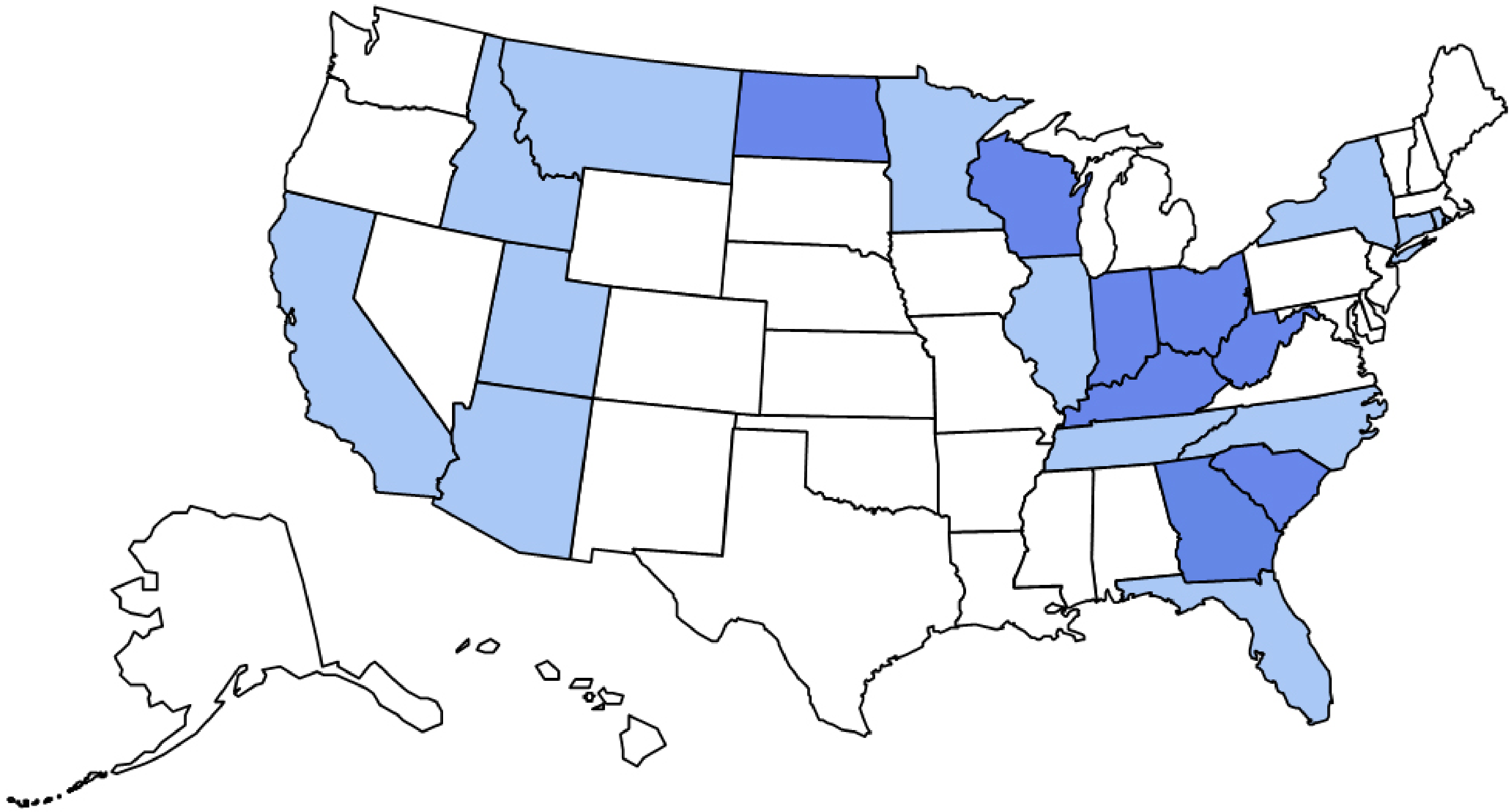


(Daan and Borbely, 1984)

- C and S are <u>independent</u> processes, that <u>interact</u> to optimize the quantity an quality of sleep.

Obesity Trends* Among U.S. Adults
BRFSS, 1985

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



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

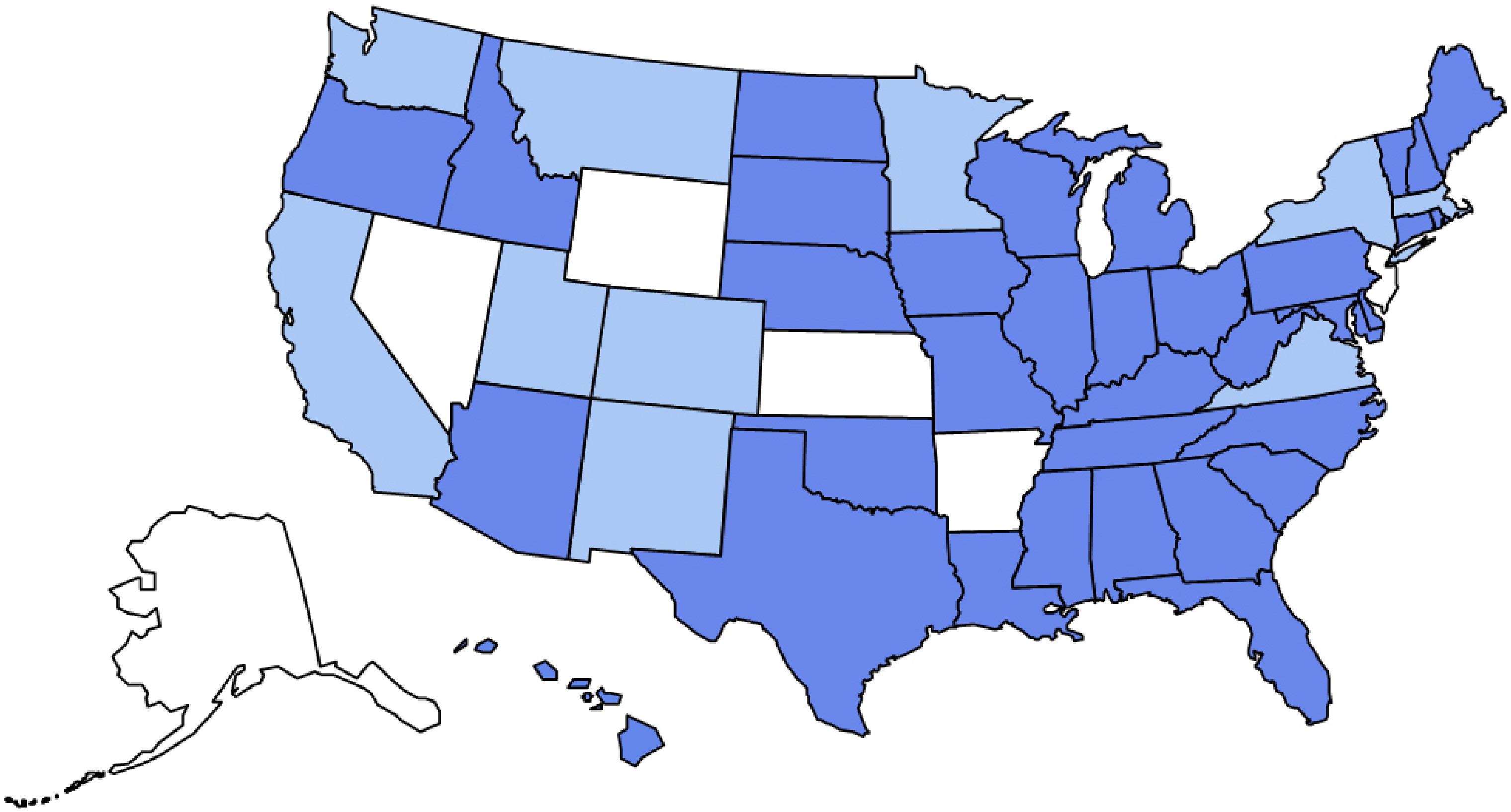
Source: Mokdad A H, et al. *J Am Med Assoc* 1999; 282:16

CENTERS FOR DISEASE CONTROL AND PREVENTION

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%

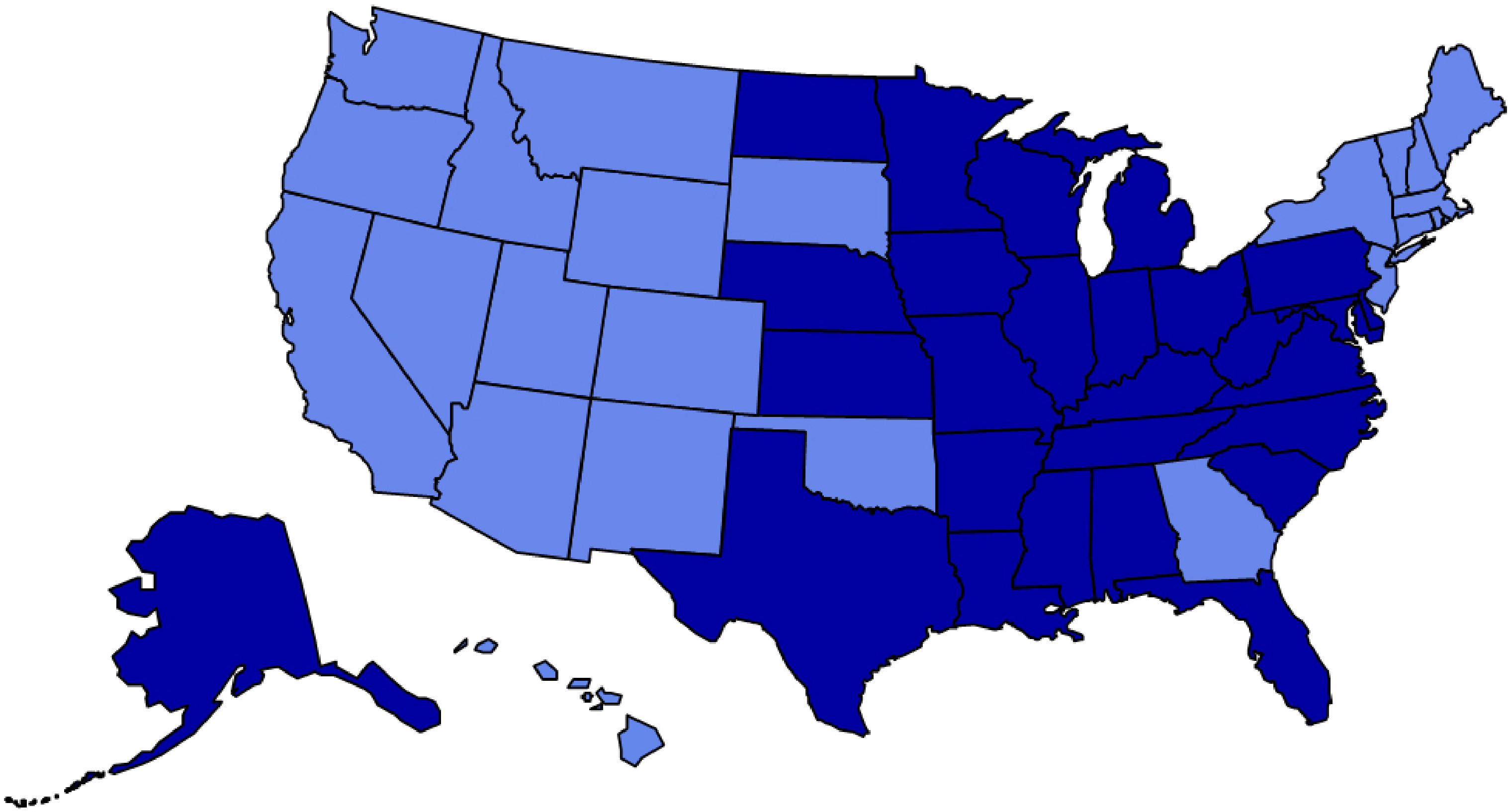
Source: Mokdad A H, et al. *J Am Med Assoc* 1999; 282:16

CDC
Centers for Disease Control and Prevention

Obesity Trends* Among U.S. Adults

BRFSS, 1995

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



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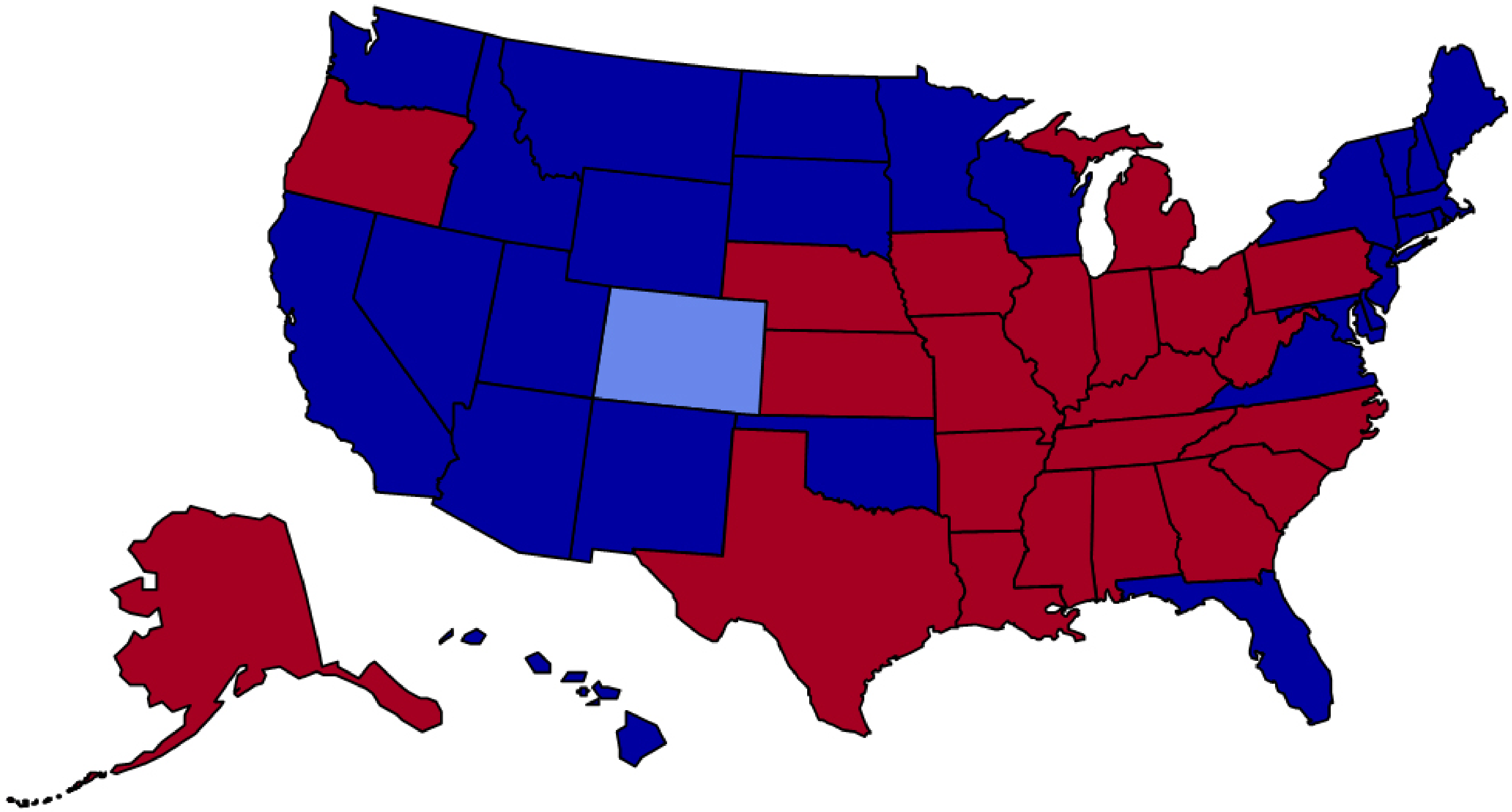
Source: Mokdad A H, et al. *J Am Med Assoc* 1999; 282:16

CENTERS FOR DISEASE CONTROL AND PREVENTION

Obesity Trends* Among U.S. Adults

BRFSS, 2000

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



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

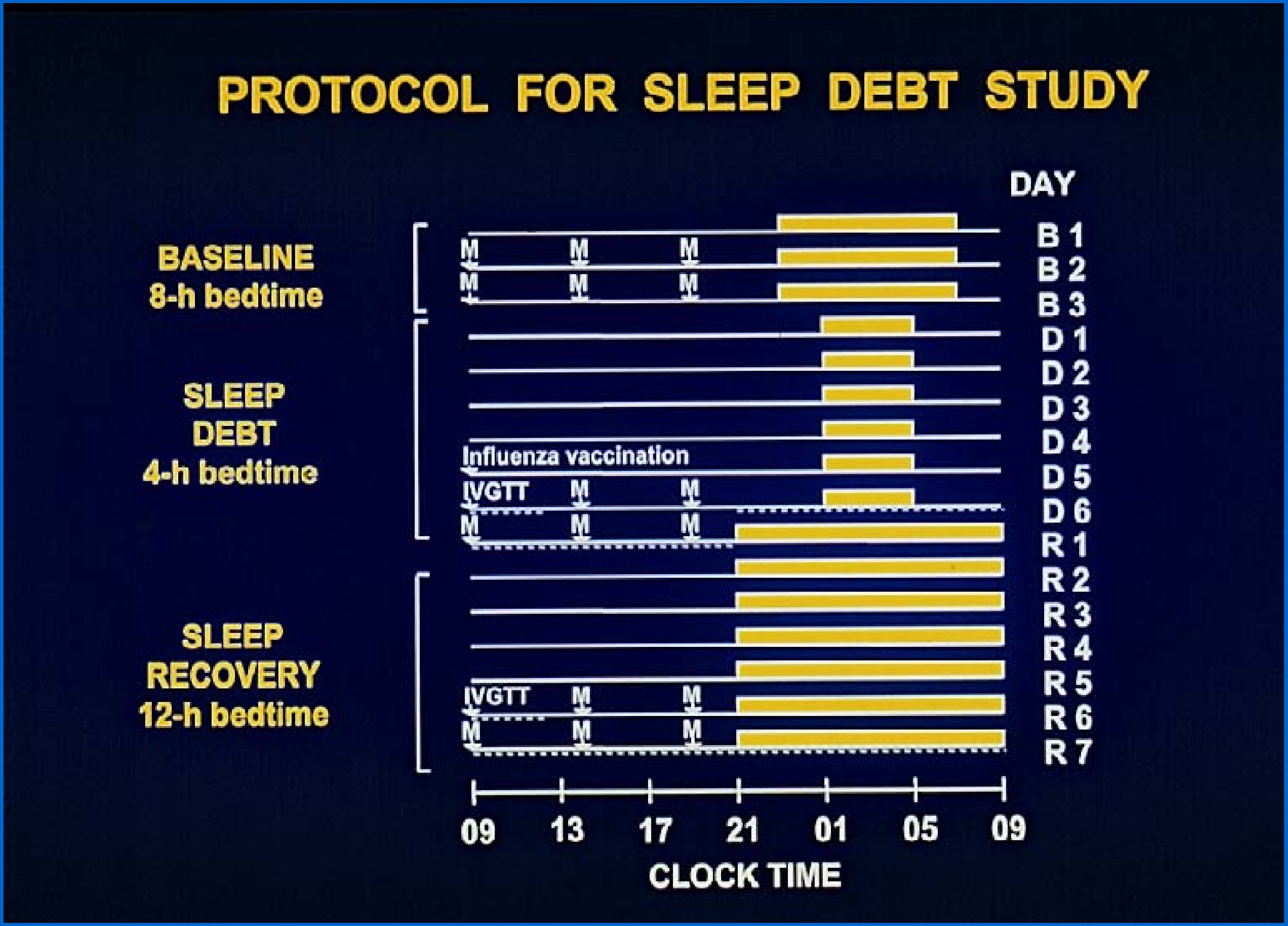
Source: Mokdad A H, et al. *J Am Med Assoc* 1999; 282:16

CDC
Centers for Disease Control and Prevention

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.

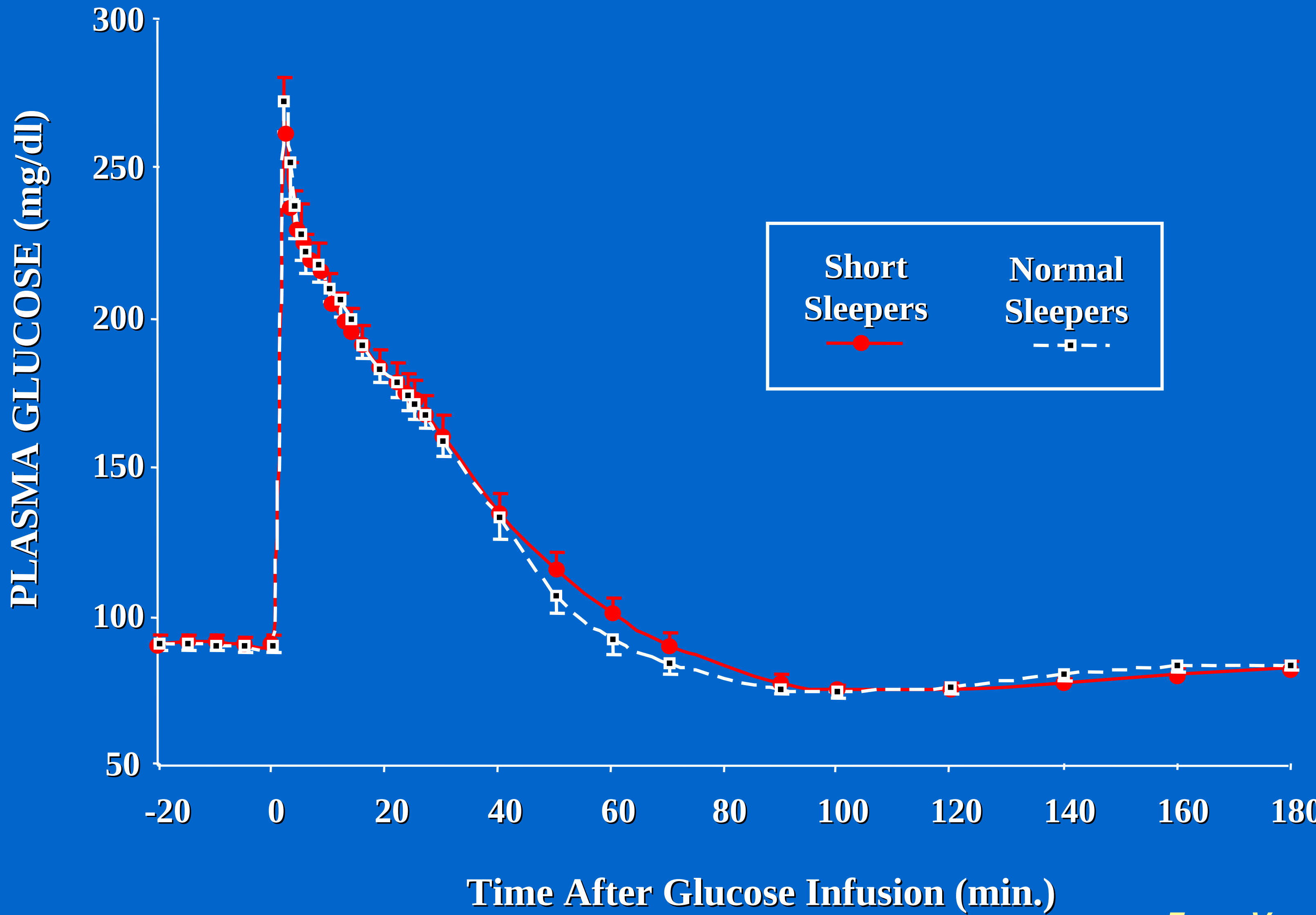
Importance of Sleep for Obesity, Diabetes and CVD

Eve Van Cauter Group at
University of Chicago
1999



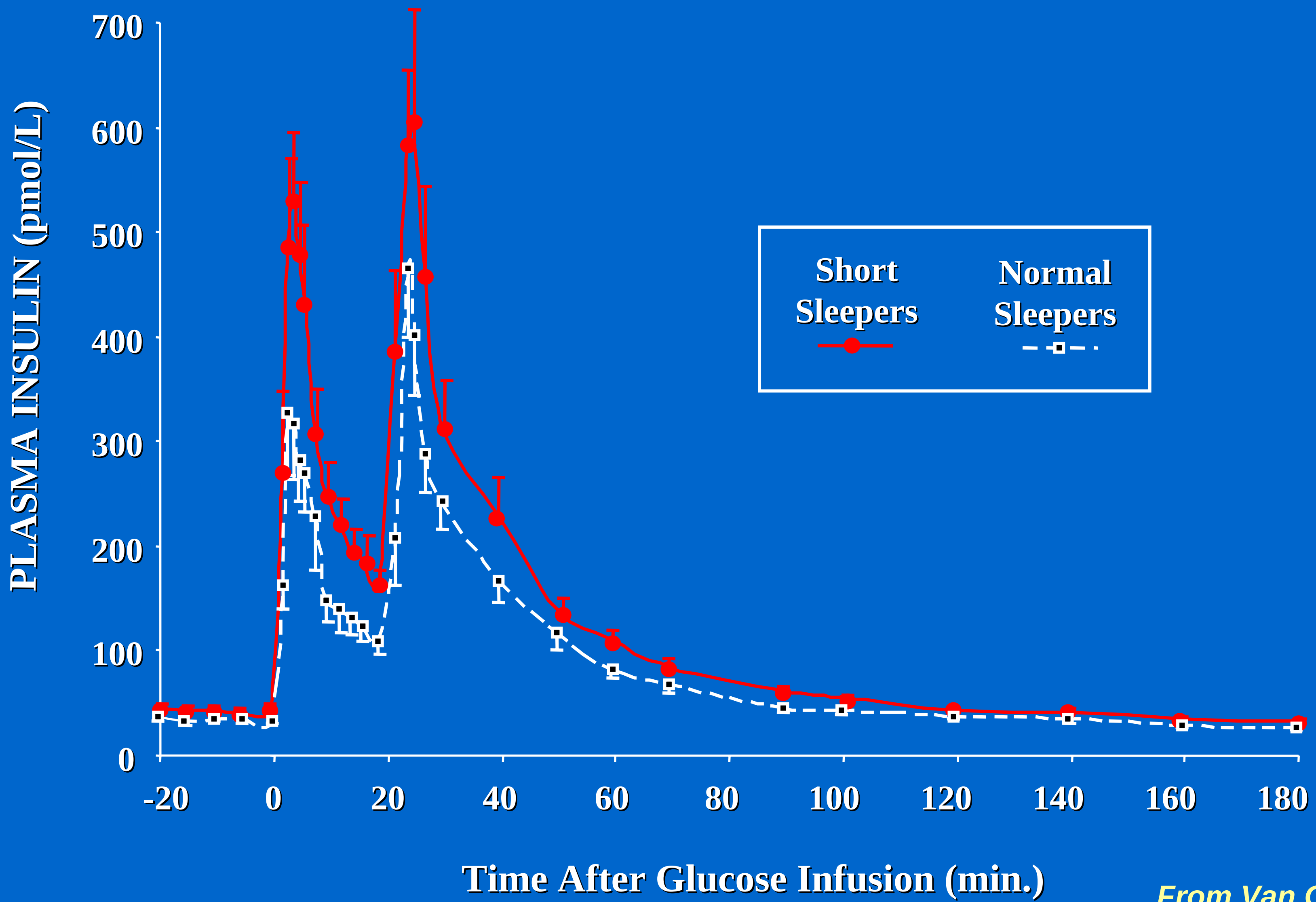
From Van Cauter

IVGTT: Glucose

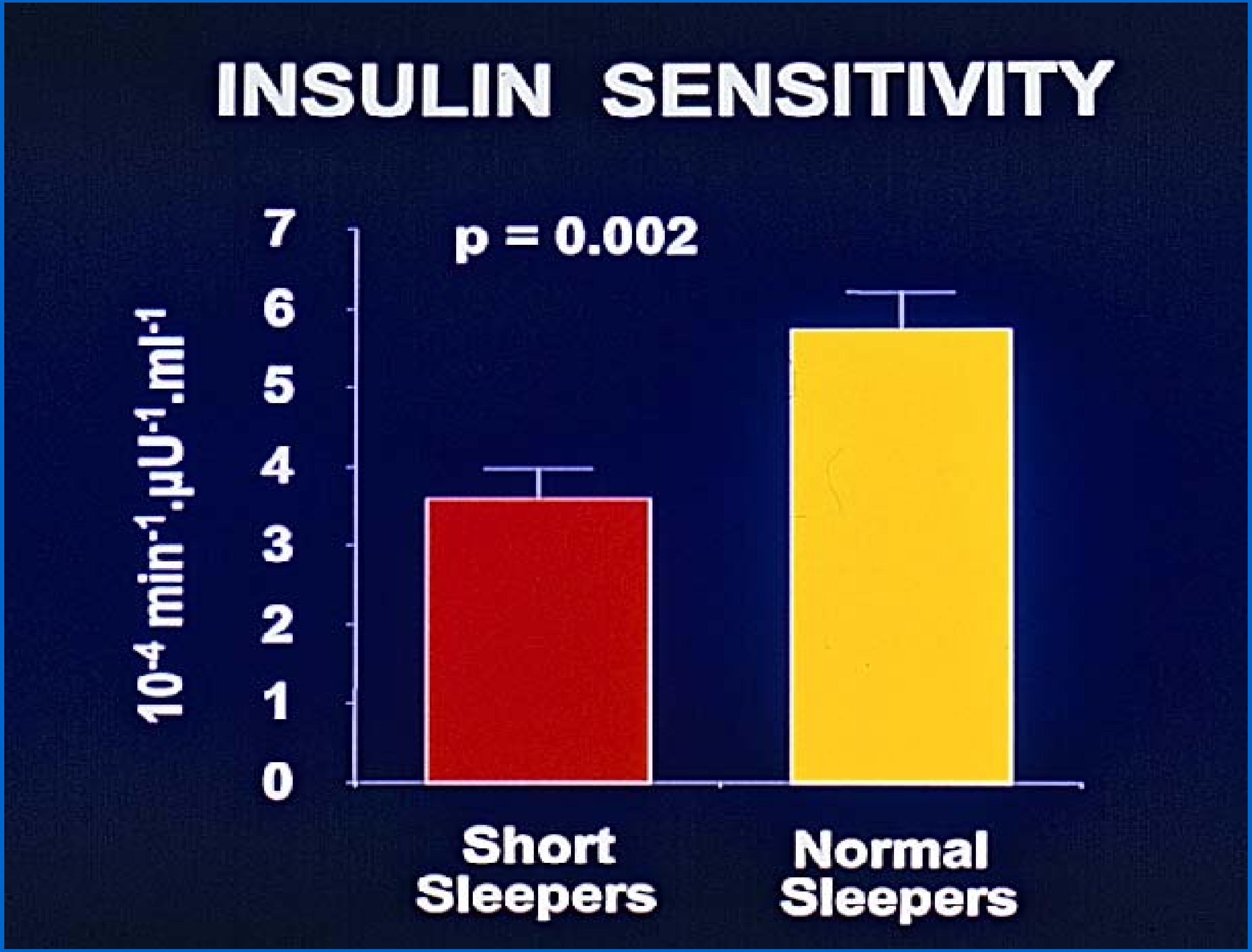


From Van Cauter

IVGTT: Insulin



From Van Cauter



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

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

* 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%

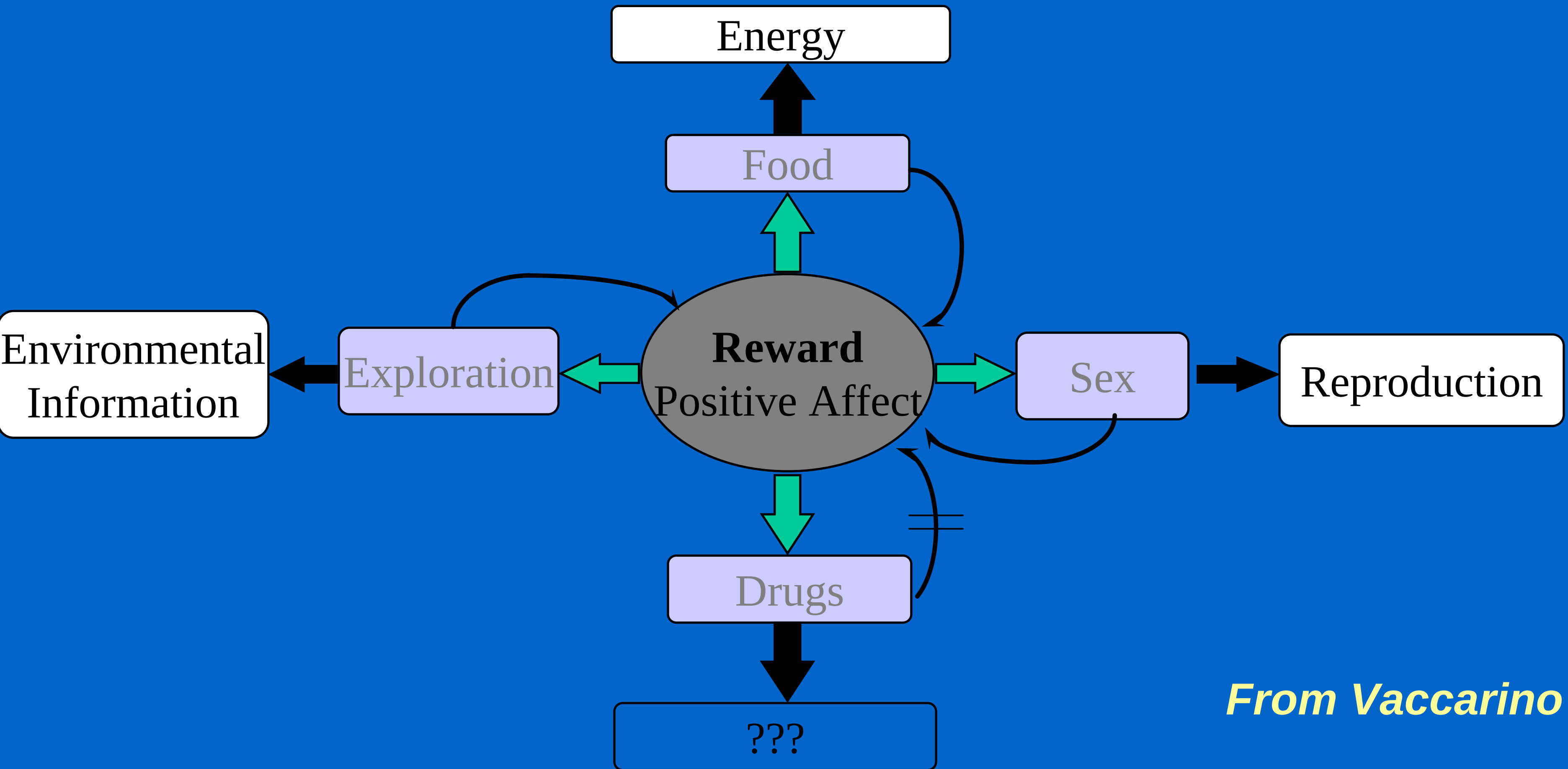
Salty foods - 45%

Starchy foods - 33%

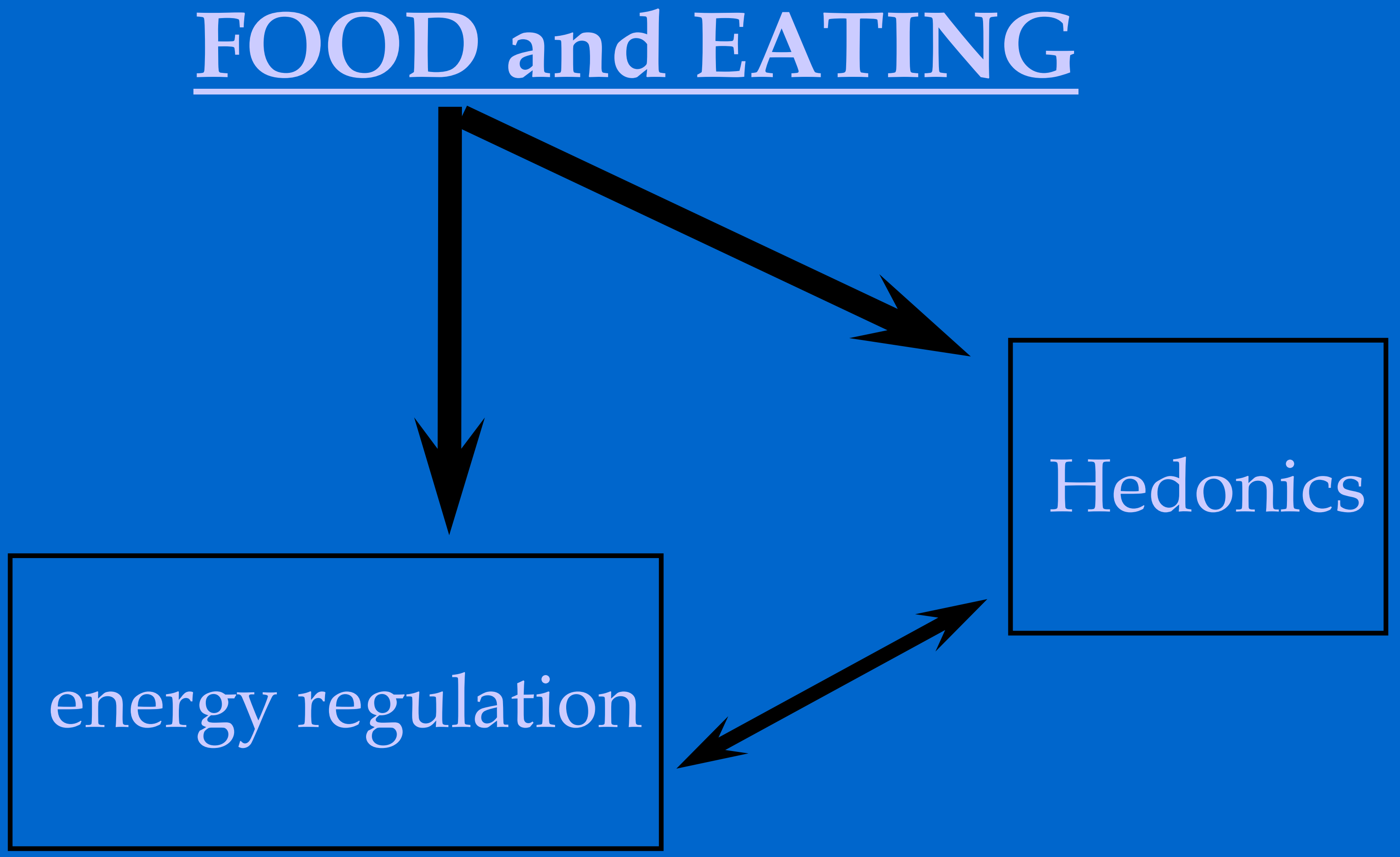
Spiegel et al., 2004

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



From Vaccarino

Links Between Food *Reward* and Drug *Reward*:

Evidence from Individual Differences in Reward and Dopamine Sensitivity

From Vaccarino

SLEEP

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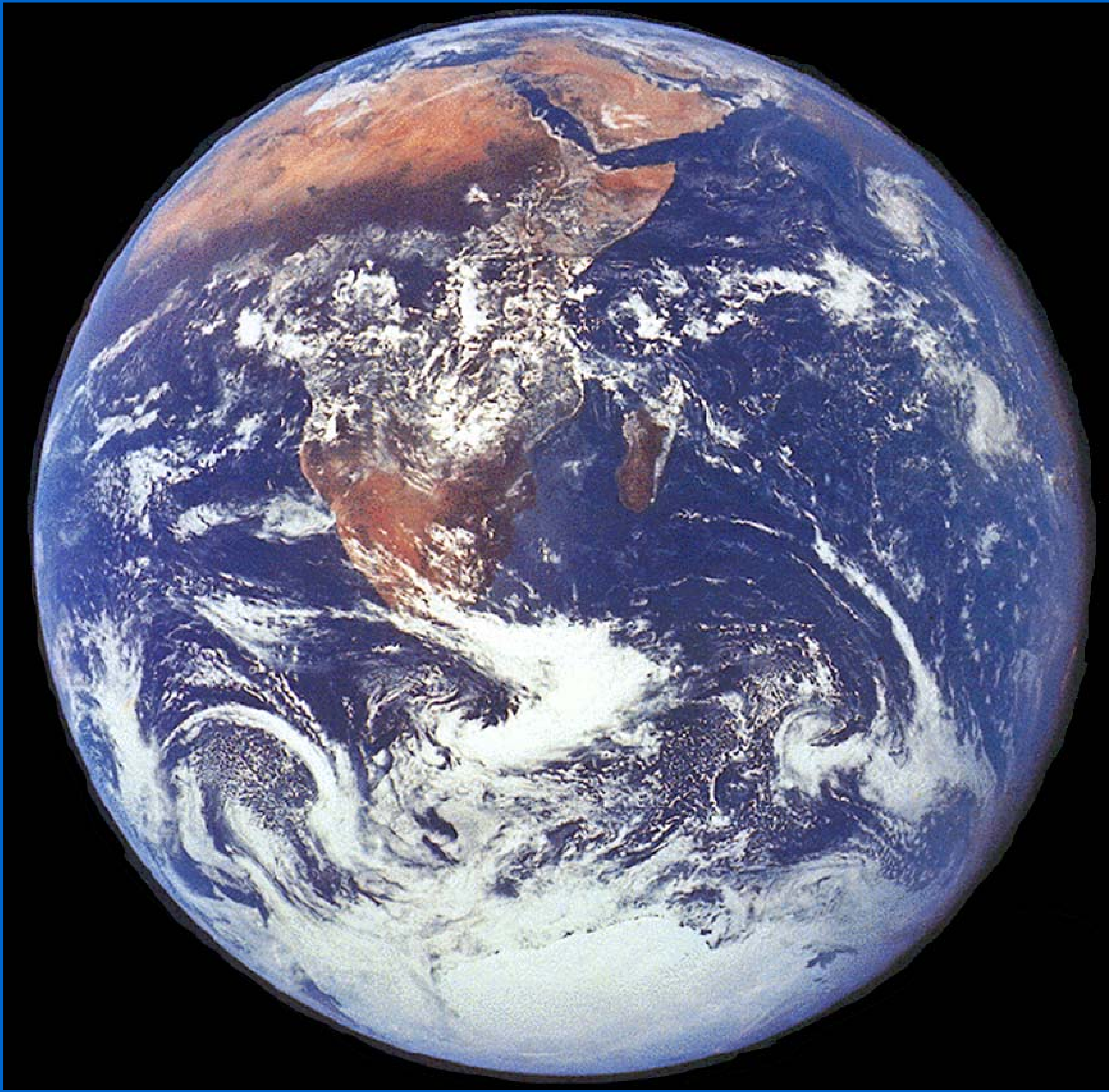
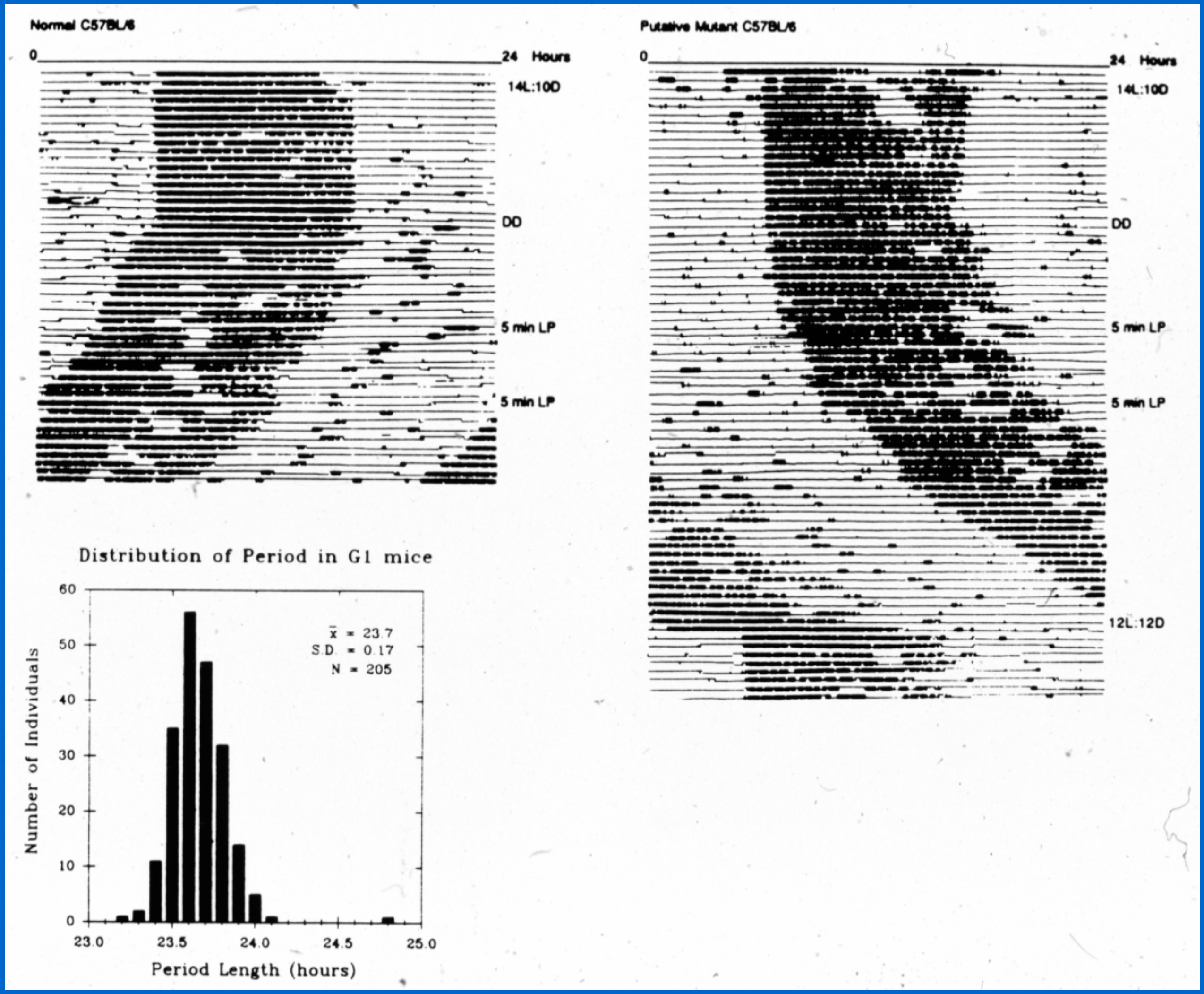
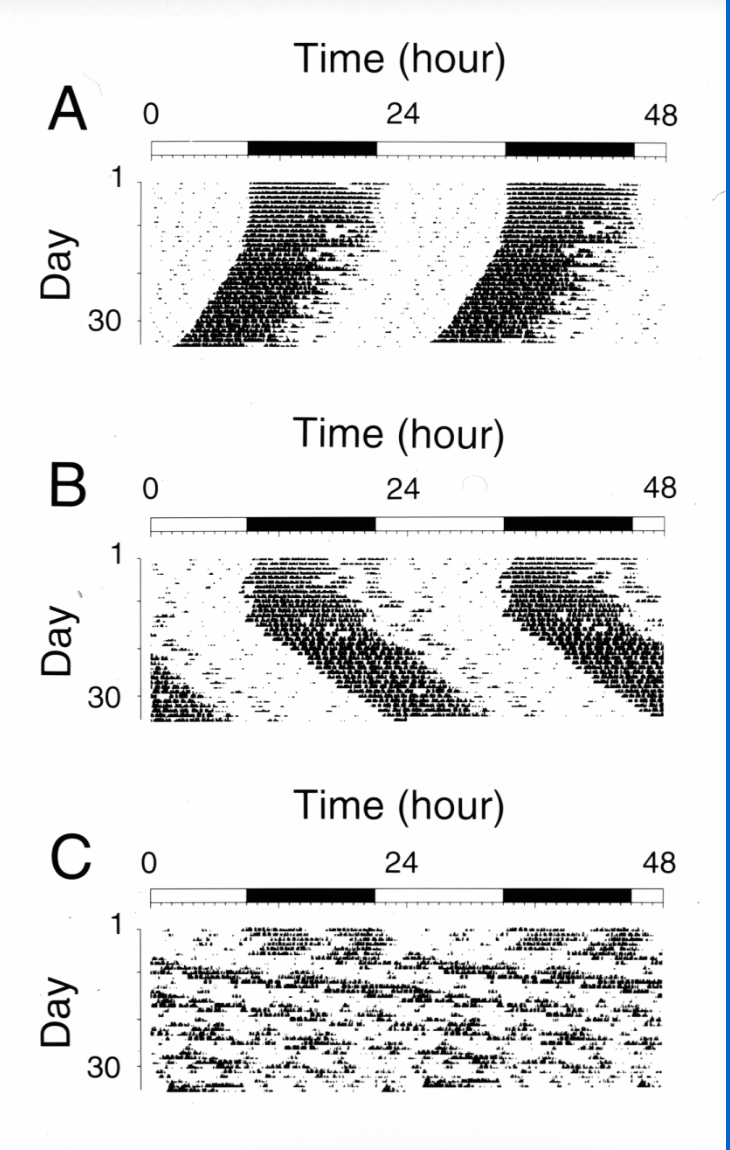
BEGINNING



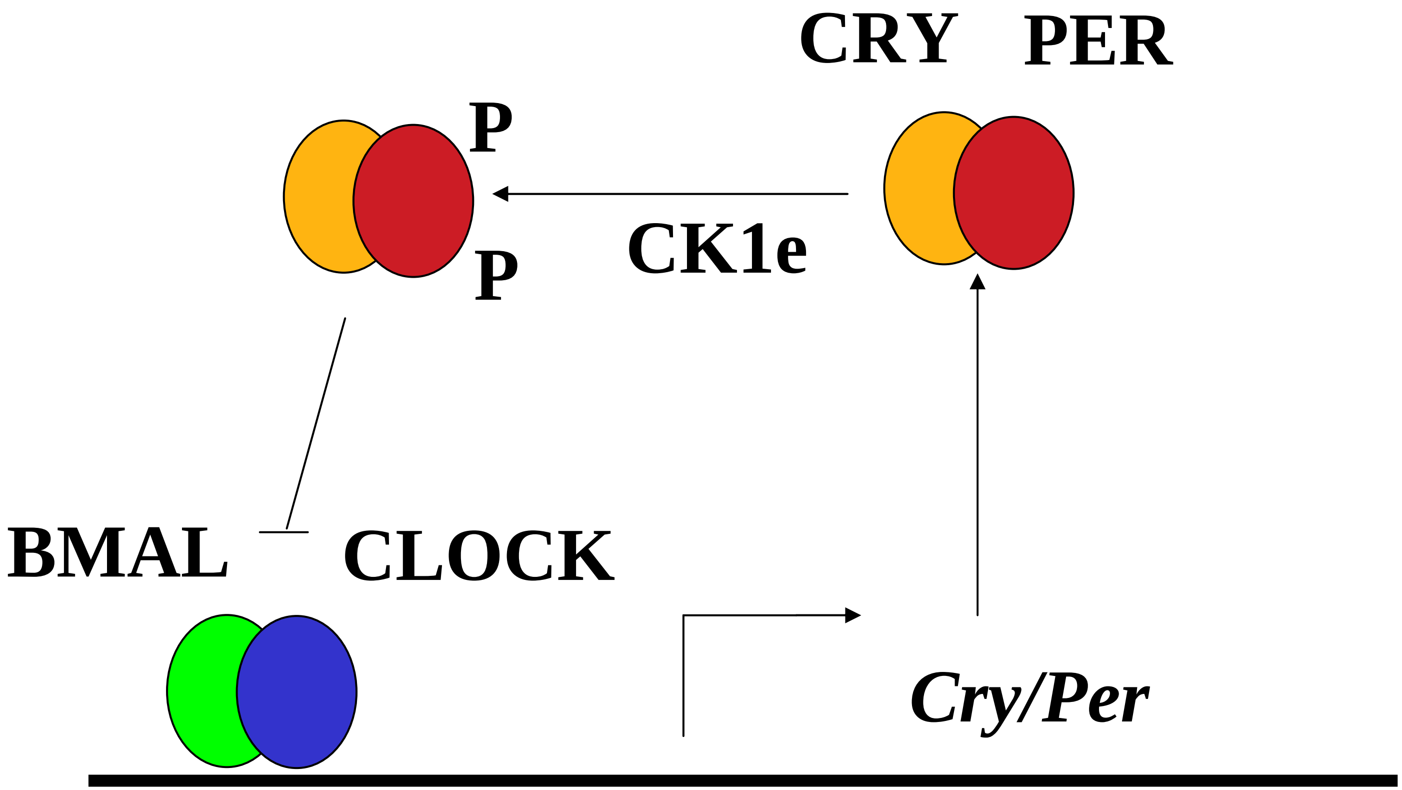
Discovery of the Mutant



Clock is a semidominant mutation



Discovery of Clock Gene Led to Discovery of <u>Many</u> Clock Genes



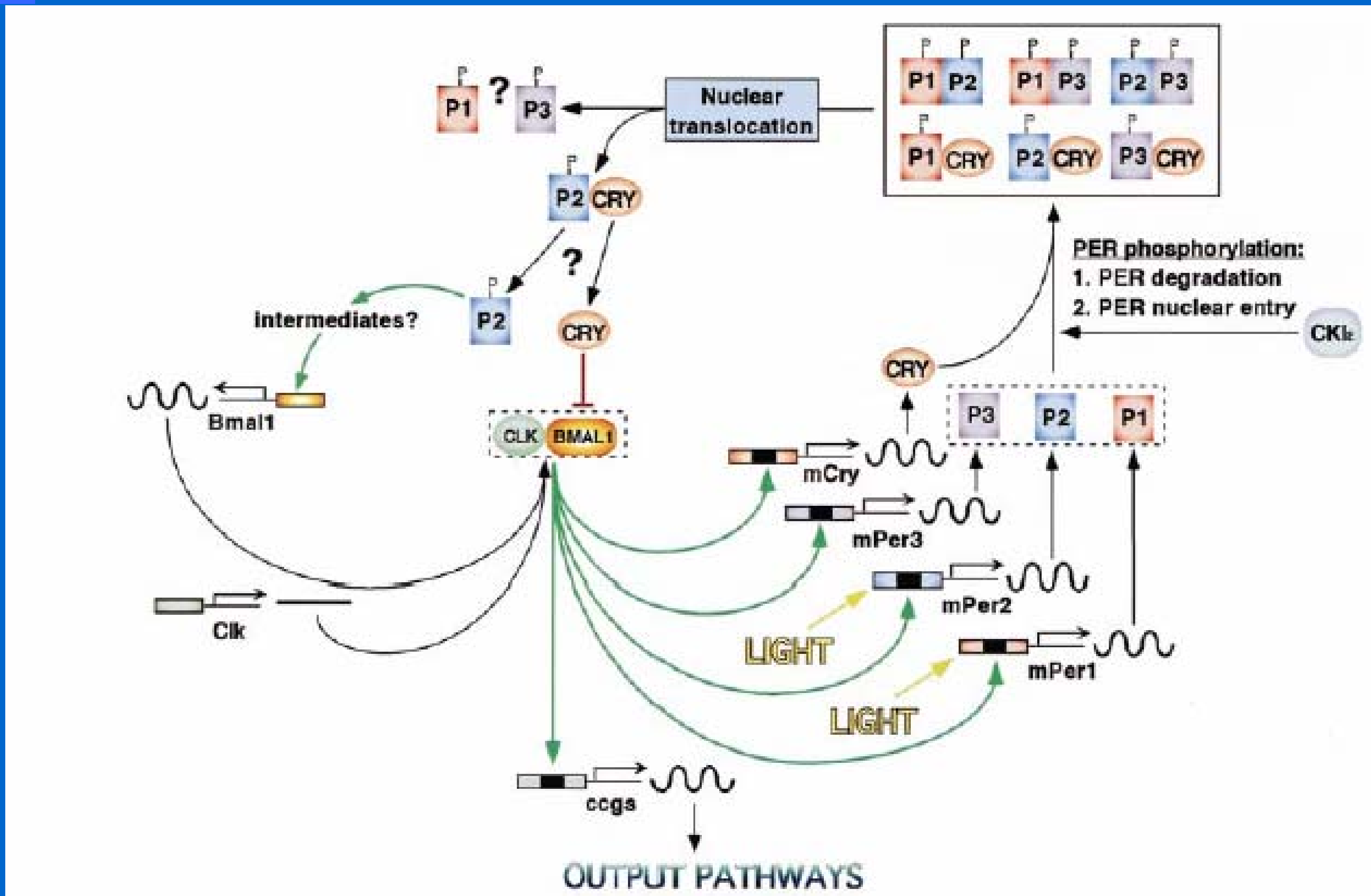
Liver Has Rhythm

Fred W. Turek and Ravi Allada

Hepatology, April 2002

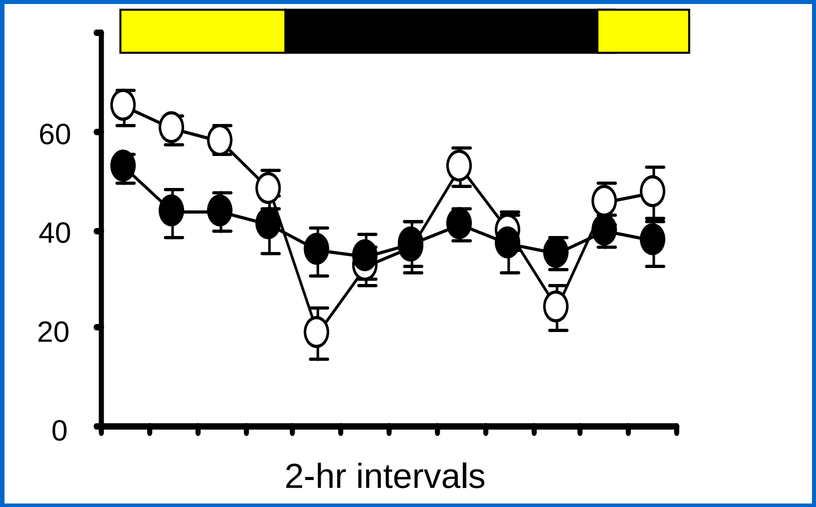
Discovery of Clock Gene Led to Discovery of Many Clock Genes

Core circadian clock genes
Transcriptional – translational feedback loop

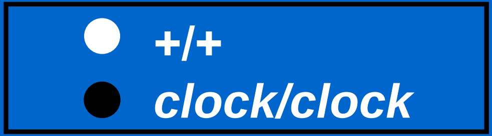


Clock/Clock mice: Baseline sleep

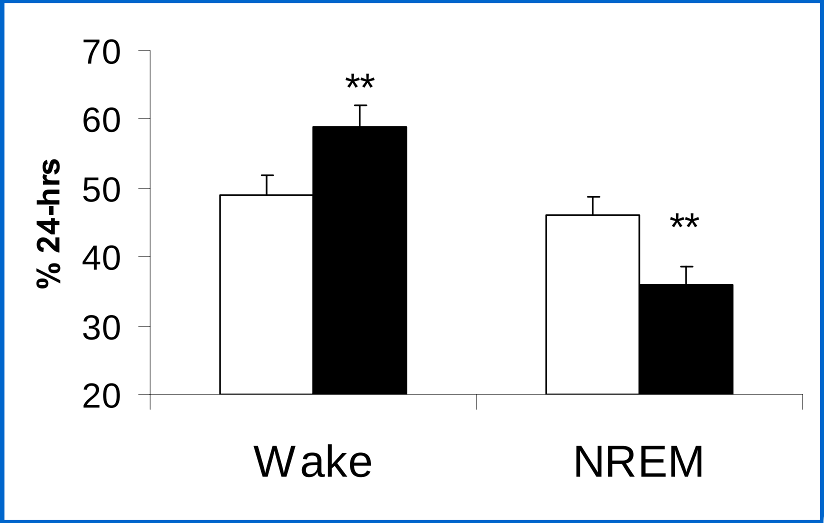
Reduced amplitude of sleep-wake cycle (NREM %)



(Easton, 2004)



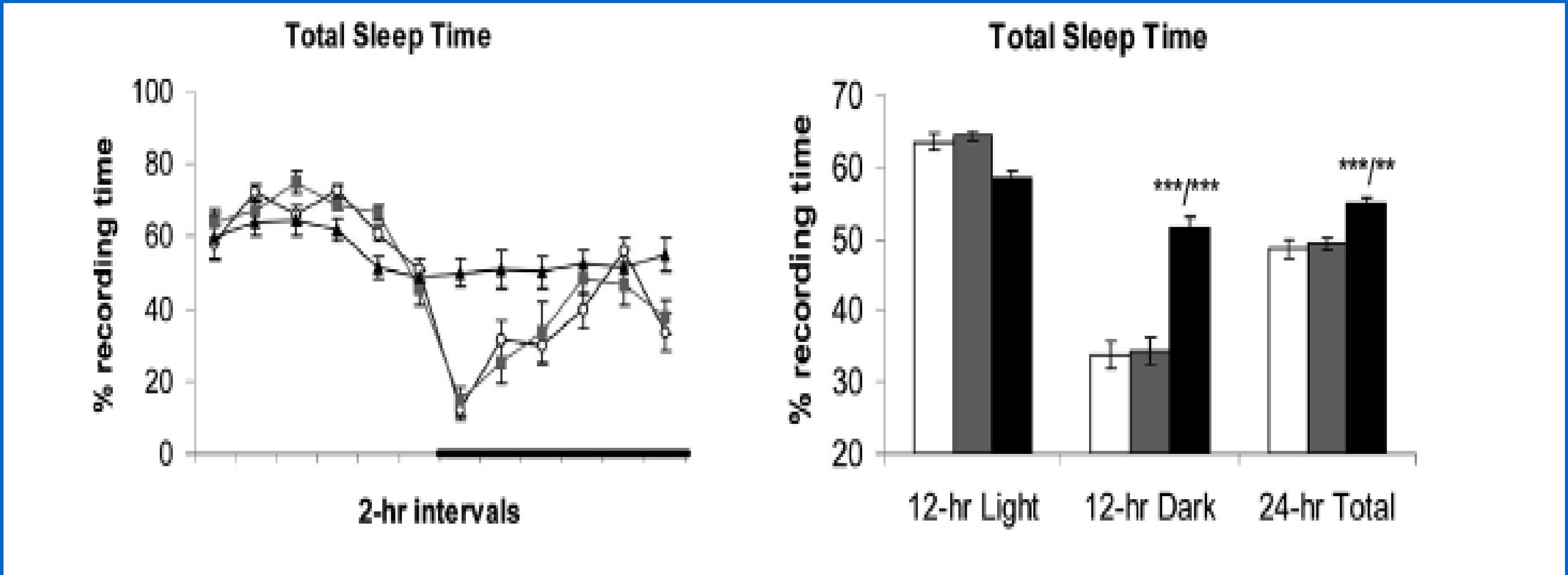
Increased wake time (+ 2 hrs/day)



(Naylor et al., 2000)

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

Circadian clock genes influence total sleep amount, sleep consolidation, and sleep homeostasis

	24-hr Wake %	24-hr NREM %	24-hr REM %	Sleep Fragmentation	Bsln NREM delta power	Recovery NREM	Recovery REM	Recovery NREM delta power
Cl/Cl (Naylor et al., 2000)	↑	↓	—	—	—	↓	↓	—
BMAL1/Mop3 $^{-/-}$ (Laposky et al., 2005)	↓	↑	↑	↑	↑	↓	↓	↓
Cry 1,2 $^{-/-}$ (Wisor et al., 2003)	↓	↑	↑	↓	↑	↓	↓	↓

- Different sleep phenotypes for different circadian genes
- Phenotypes maintained in L:D and D:D

From Flies to Mice (to Humans)

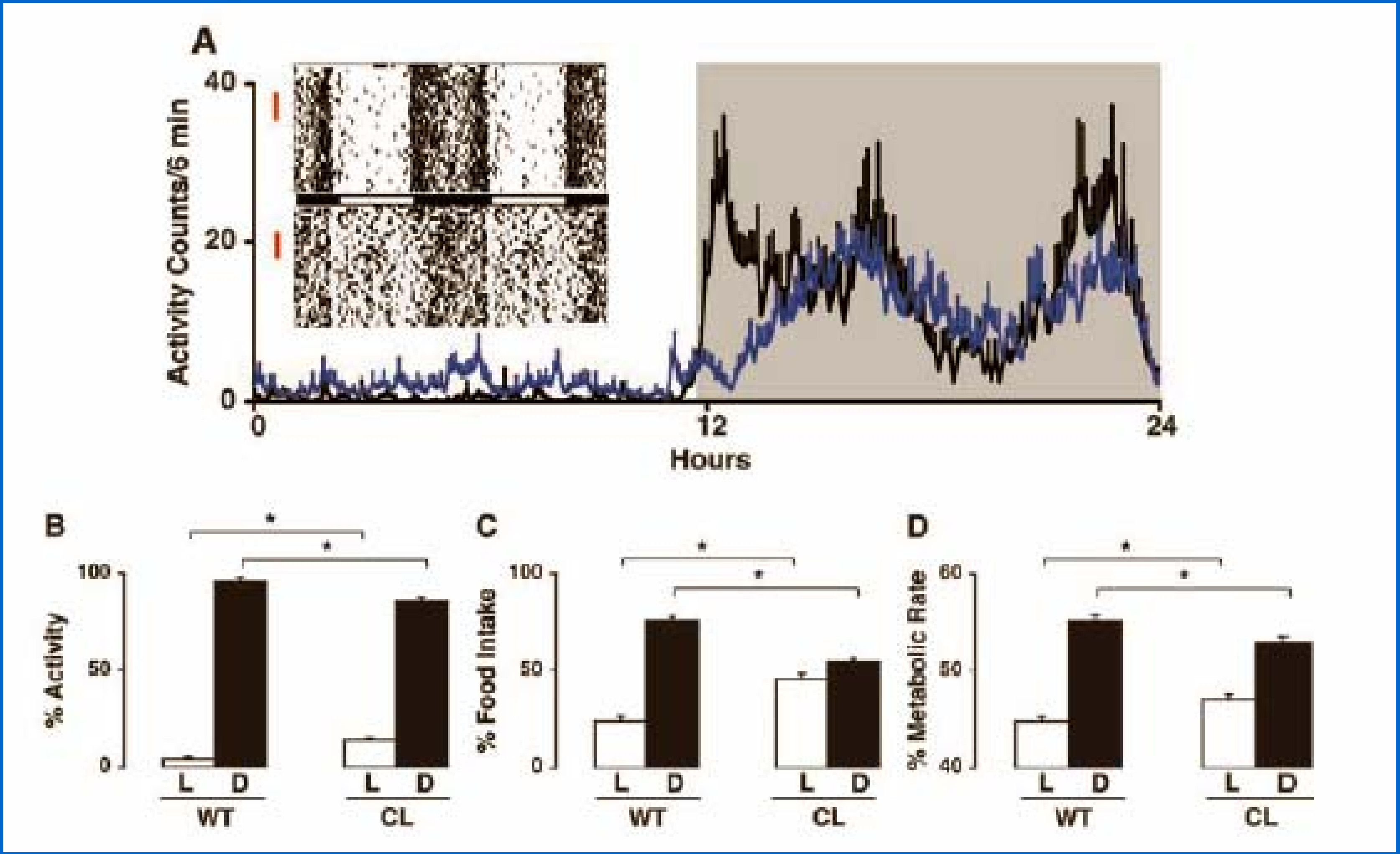
- Core clock genes influence sleep regulatory processes
- Amount, consolidation, sleep architecture, sleep rebound

Obesity and Metabolic Syndrome in Circadian *Clock* Mutant Mice

Turek FW, Joshu C, Kohsaka A, Lin E, Ivanova G, McDearmon E, Laposky A, Losee-Olson S, Easton A, Jensen DR, Eckel RH, Takahashi JS, and Bass J.

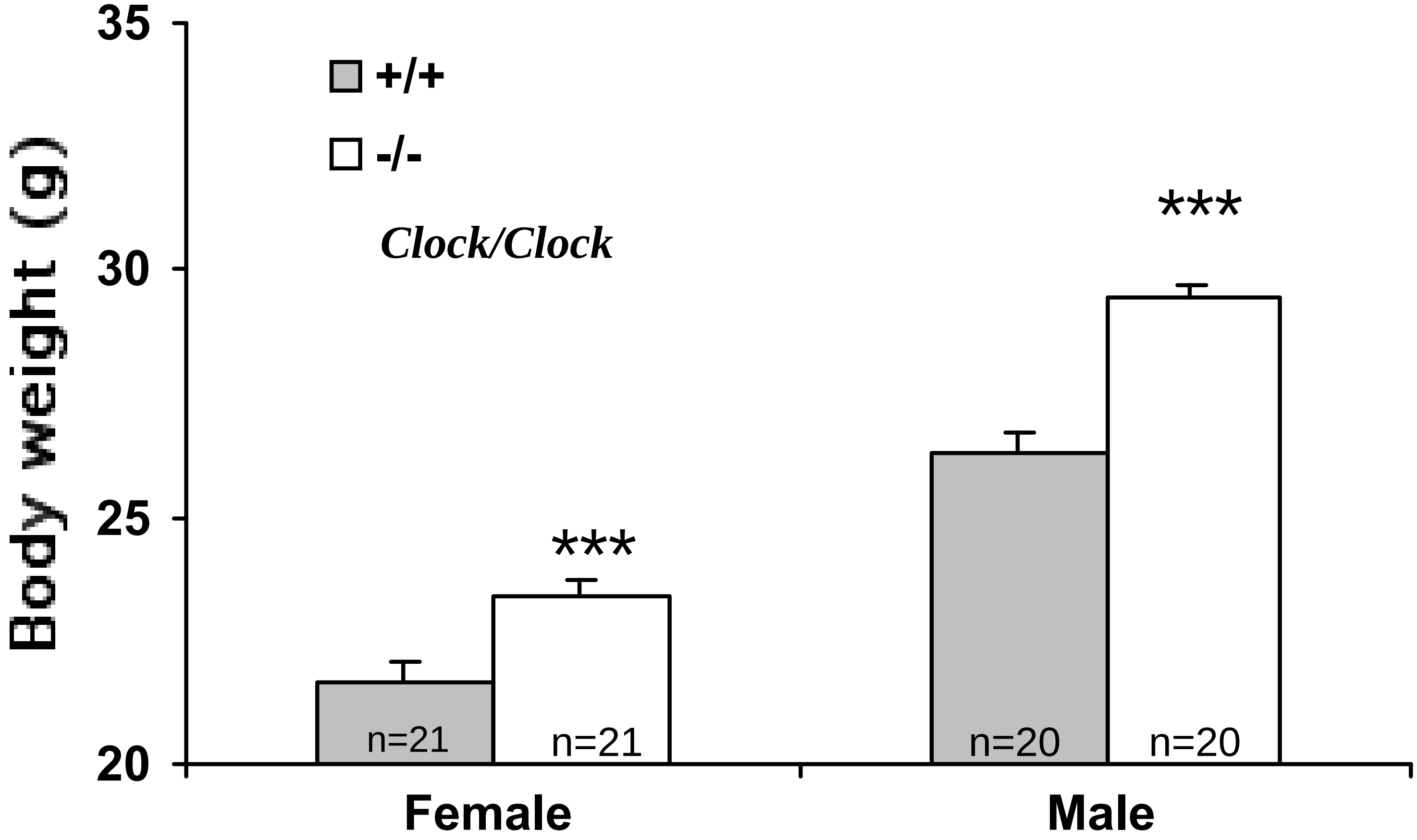
***Science* 308, 13 May 2005, p. 1043-1045**

Activity and Energy Balance



Turek et al., 2005

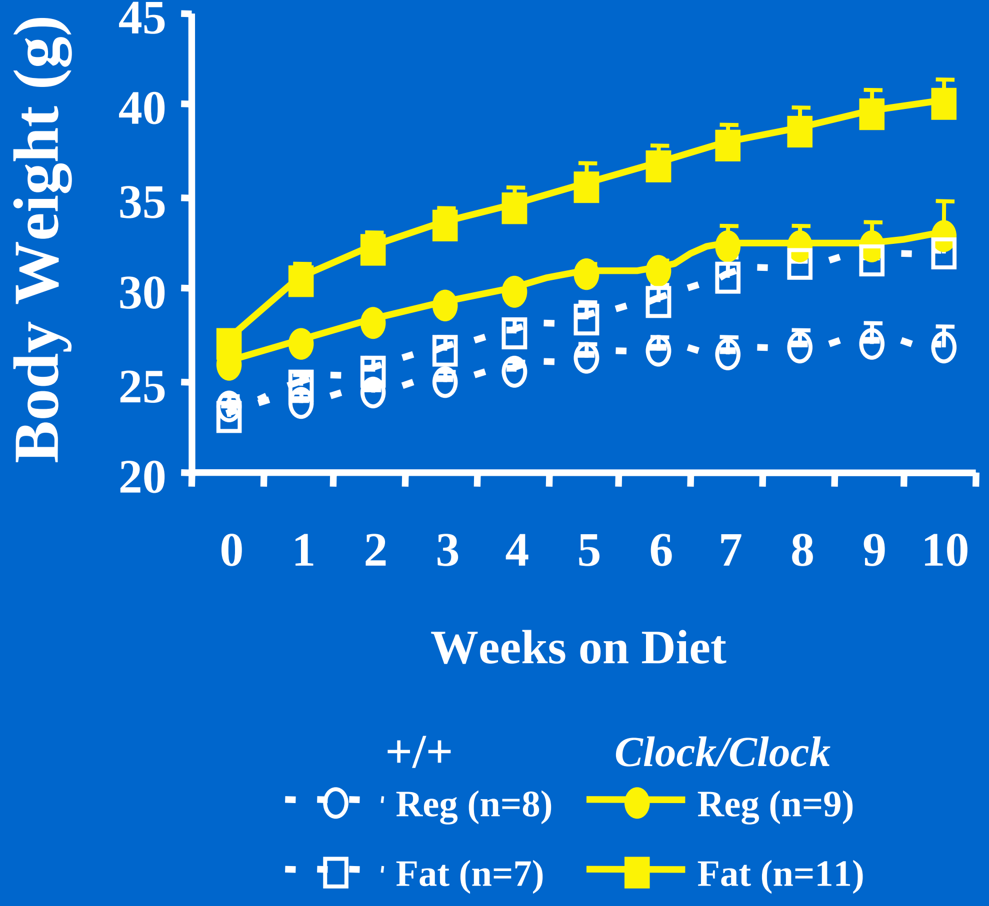
Increased Body Weight of Clock Mutants



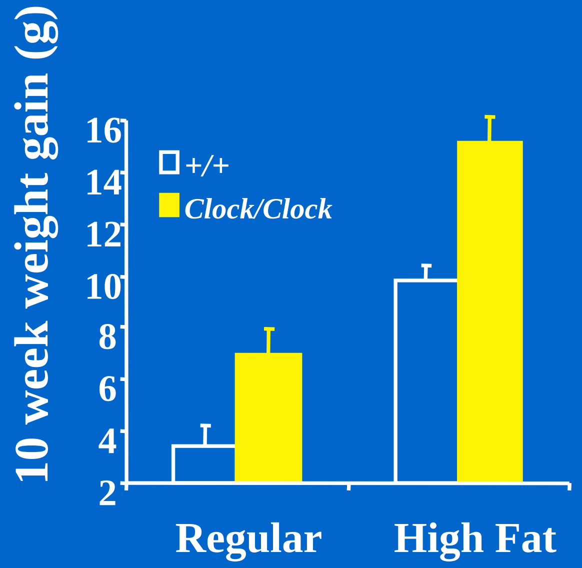
*** P < 0.001

From Science 2005

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



#3 Energy homeostasis deficit



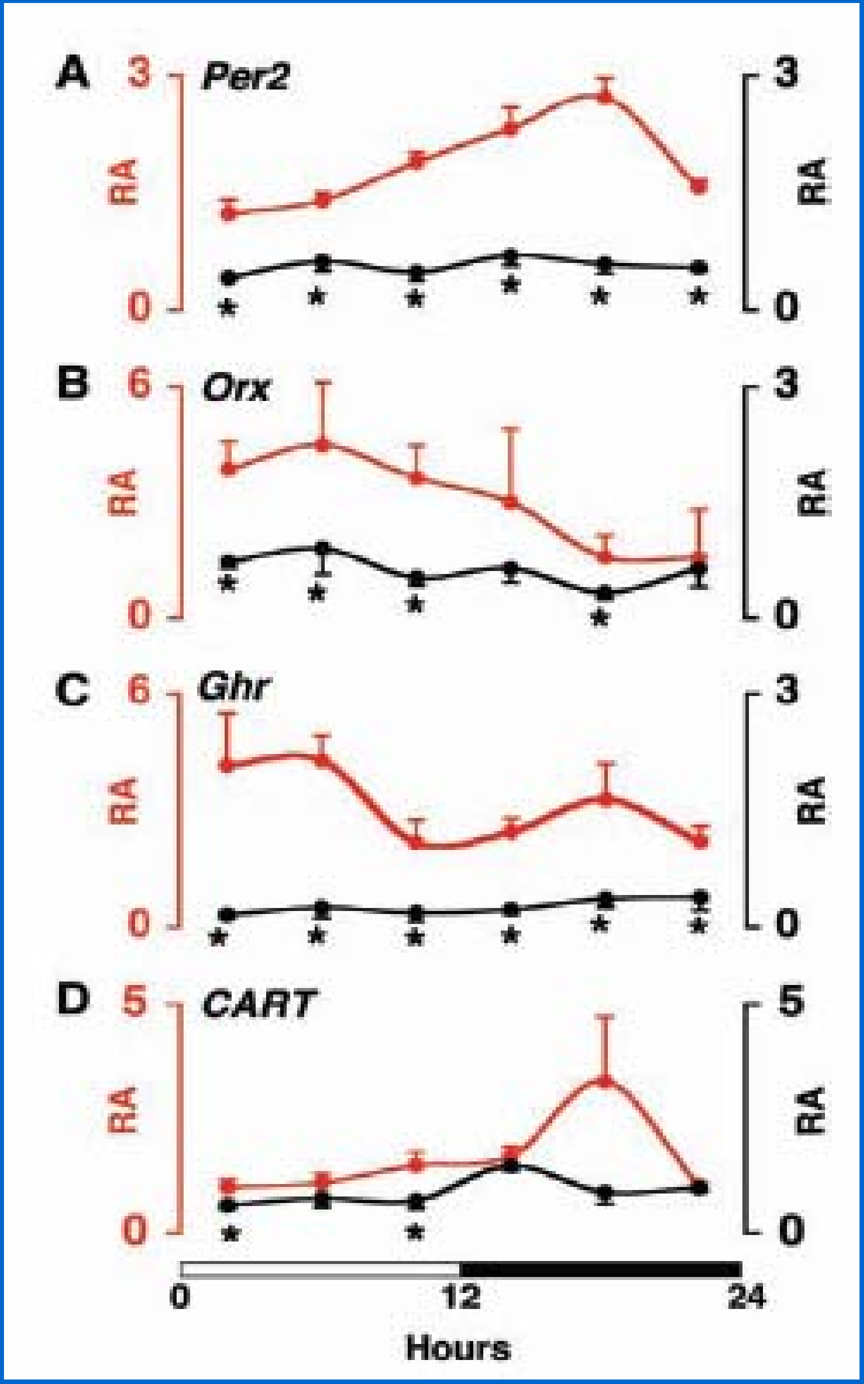
From Science 2005

Metabolic parameters	WT	*Clock*	*P* value
Triglyceride (mg/dl)	136 ± 8	164 ± 8	< 0.05
Cholesterol (mg/dl)	141 ± 9	163 ± 6	< 0.05
Glucose (mg/dl)	130 ± 5	161 ± 7	< 0.01
Insulin (ng/ml)	1.7 ± 0.3	1.1 ± 0.1	N.S.
Leptin (ng/ml)	3.4 ± 0.4	4.6 ± 0.3	< 0.05

Diurnal rhythms in the mediobasal hypothalamus

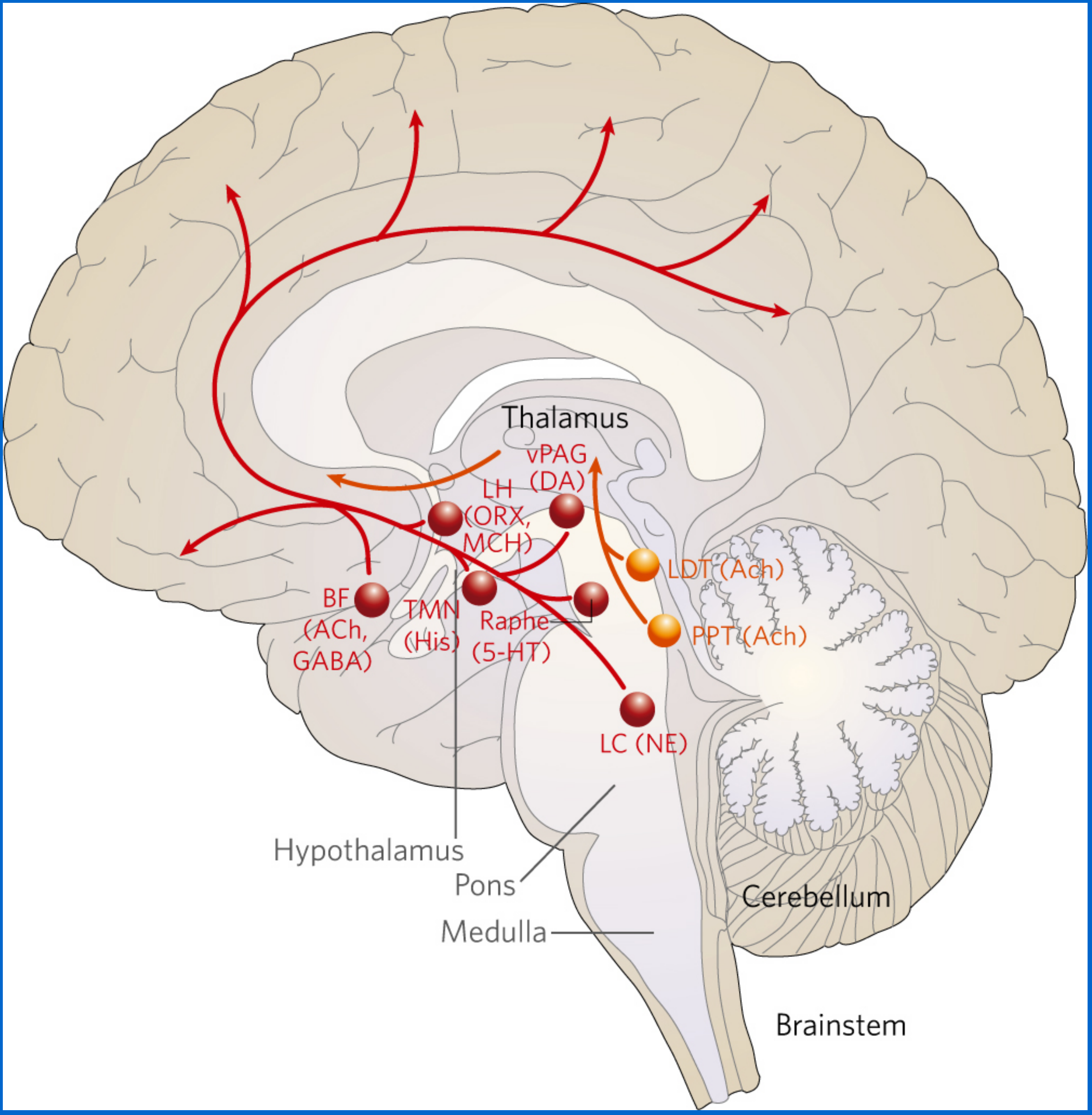
Wild-type = red

***Cl/Cl* mutant = black**



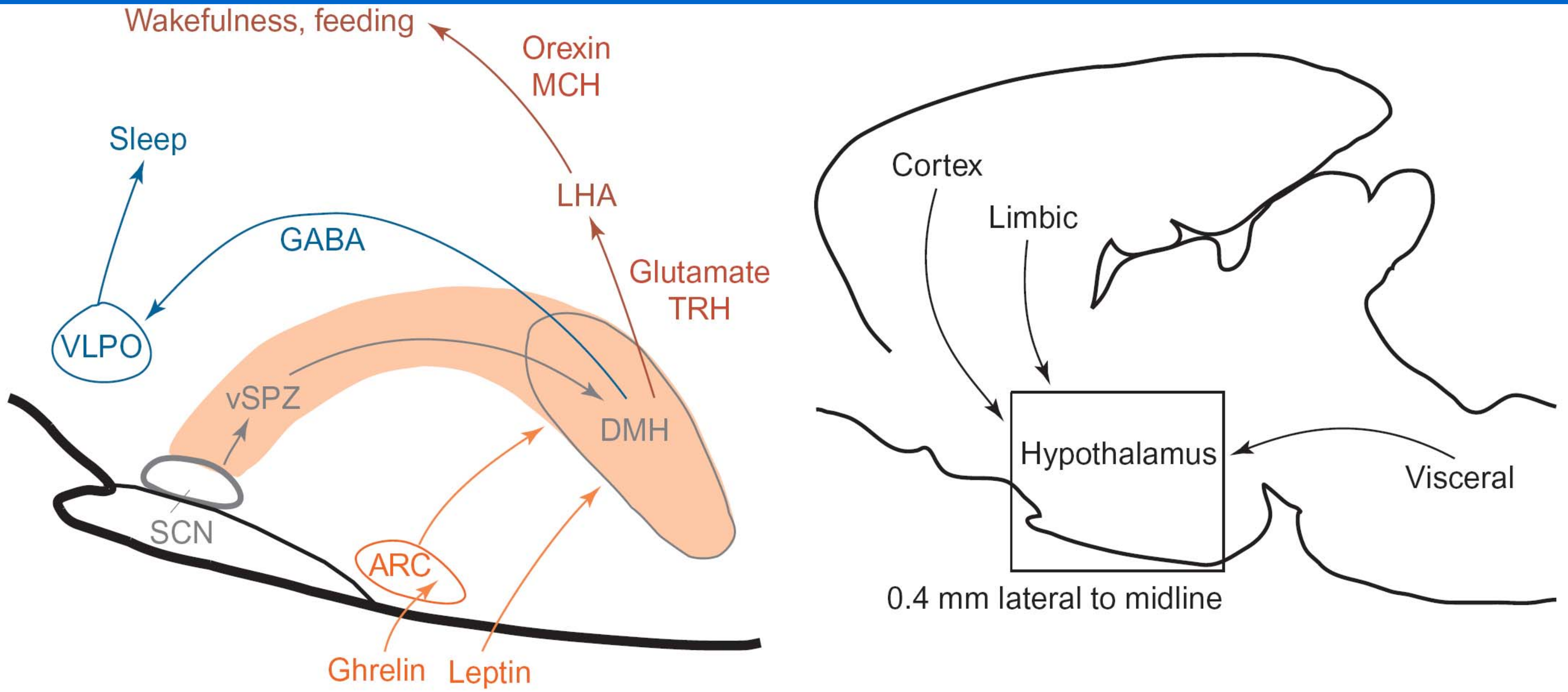
Turek et al., Science (2005)

Ascending Arousal Pathways



Saper et al., *Nature* 437:1257, 2005

Interactions of Circadian Regulation of Sleep and Feeding



Saper et al., TINS 28:152-157, 2005

Nature Medicine January 2006

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.

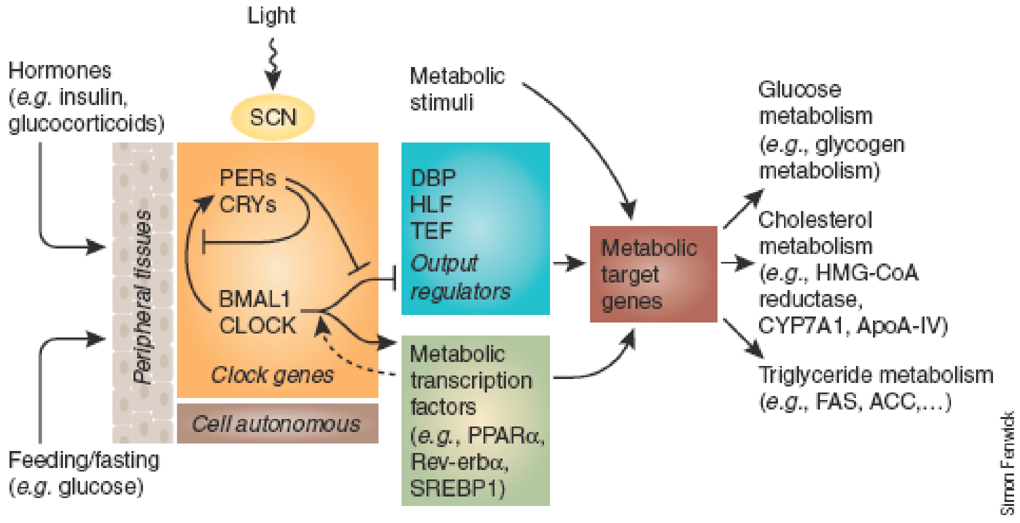
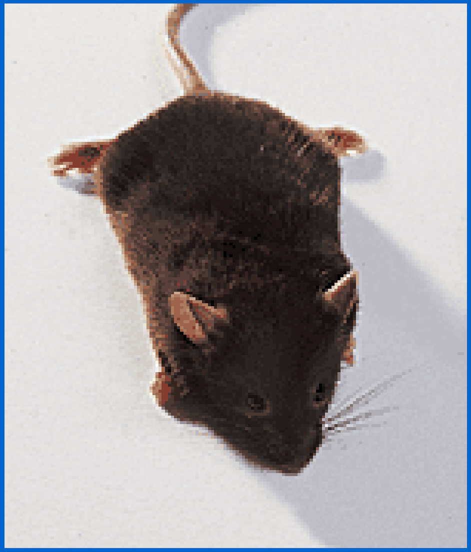


Figure 1 Transcriptional control of metabolic pathways by circadian oscillators. The molecular circadian oscillator is composed of two coupled feedback loops—Per-Cry and Clock-Bmal1—that regulate each other rhythmically. These feedback loops also control the expression of downstream transcription factors 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



Wild type

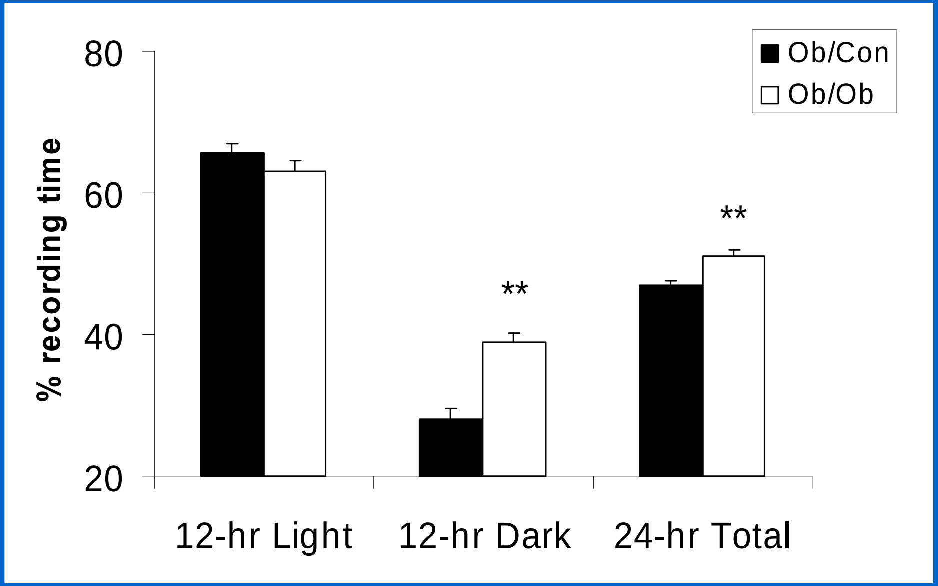
ob/ob

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

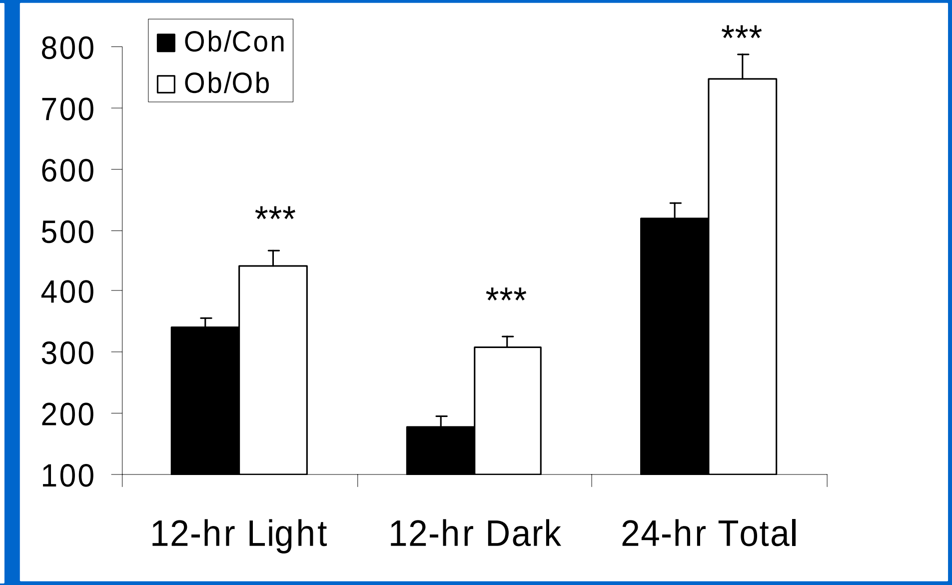
Altered sleep regulation in *ob/ob* mice

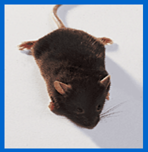
- Increased sleep time (+ 1 hour/day)
- Increased sleep fragmentation

Total sleep time



Stage Shifts





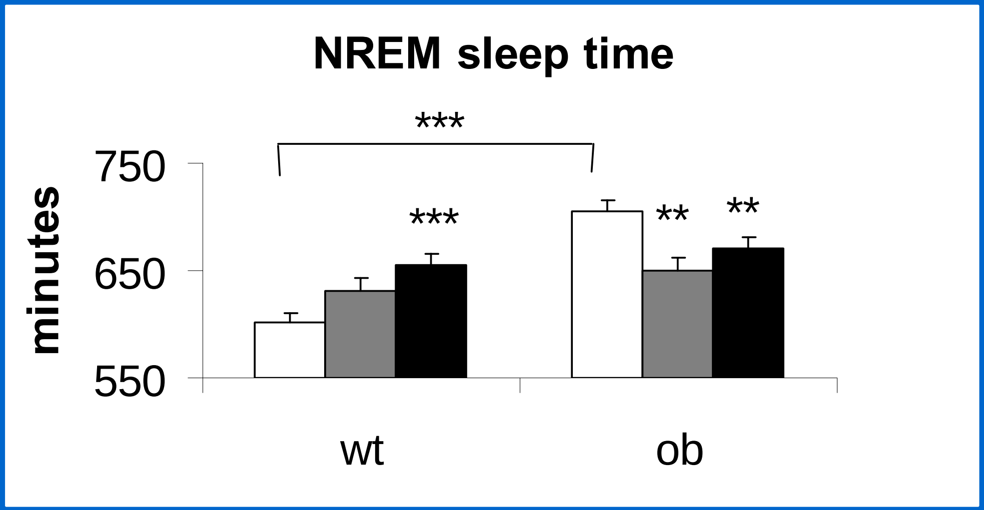
Wild type

ob/ob

Laposky et al., (2006), Am J Physiol

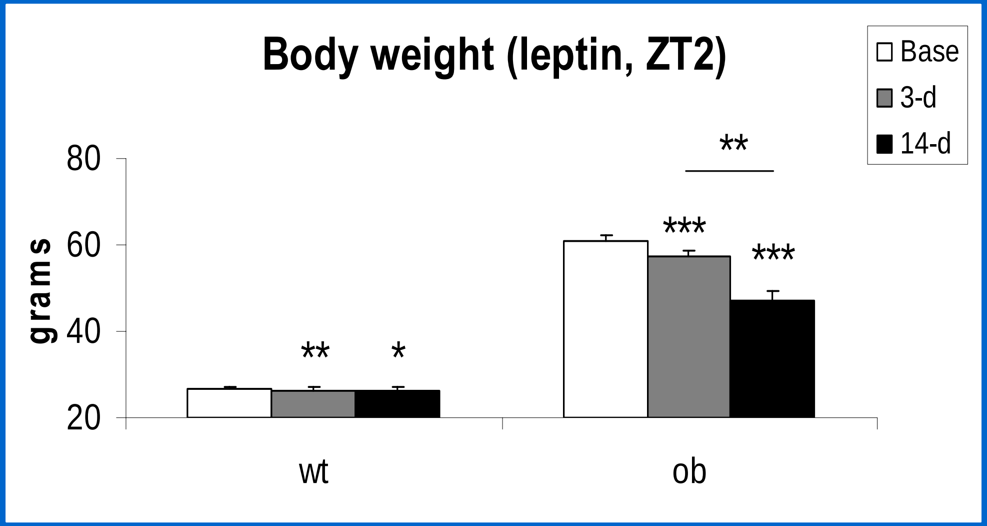
Effect of leptin repletion on sleep in *ob/ob* mice

Leptin normalizes NREM sleep time between genotypes



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

Sleep effects do not correlate with body weight



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

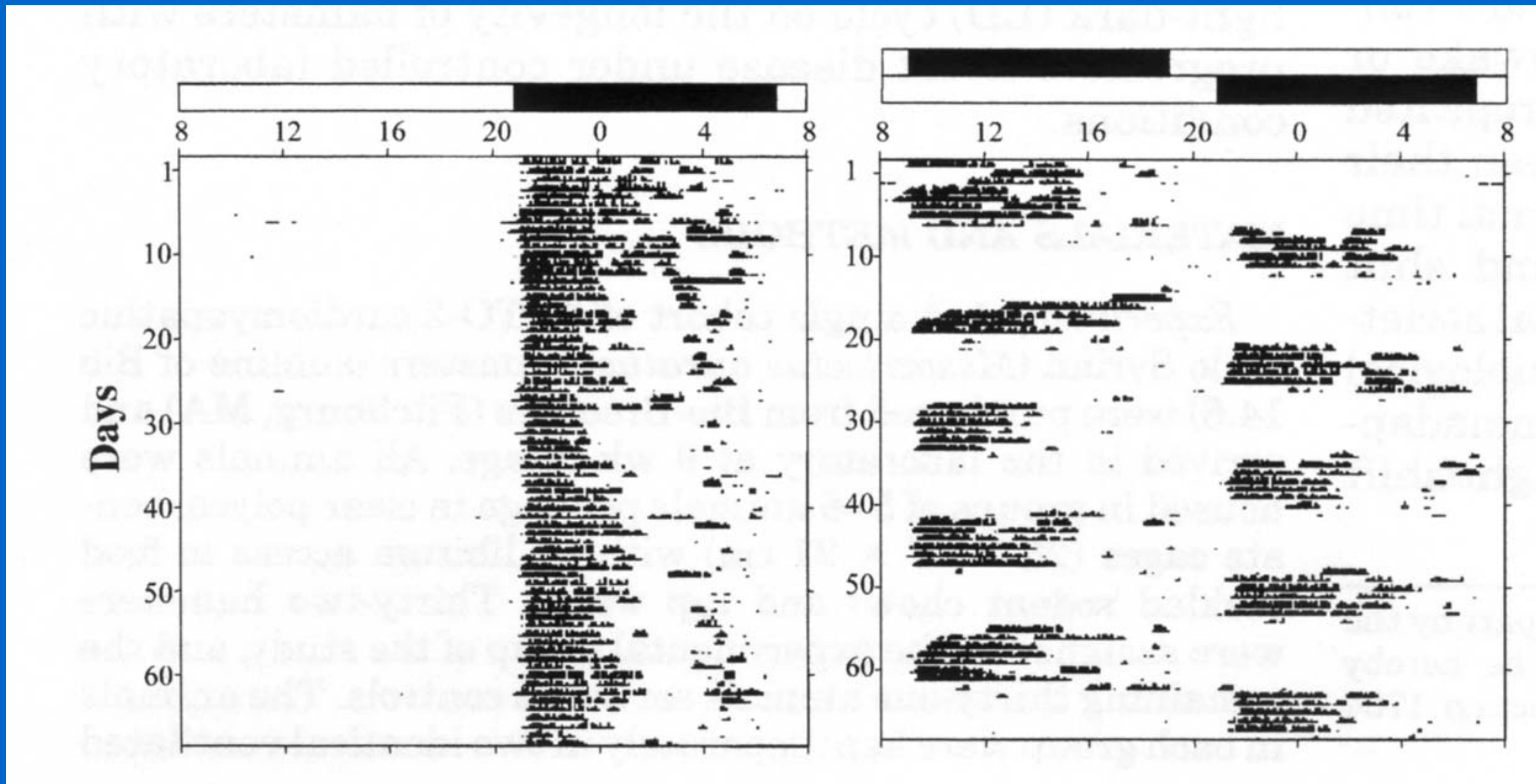
Sleepless in America: A Pathway to Obesity and the Metabolic Syndrome?

Joseph Bass and Fred W. Turek

Archives of Internal Medicine, 2005

“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.”

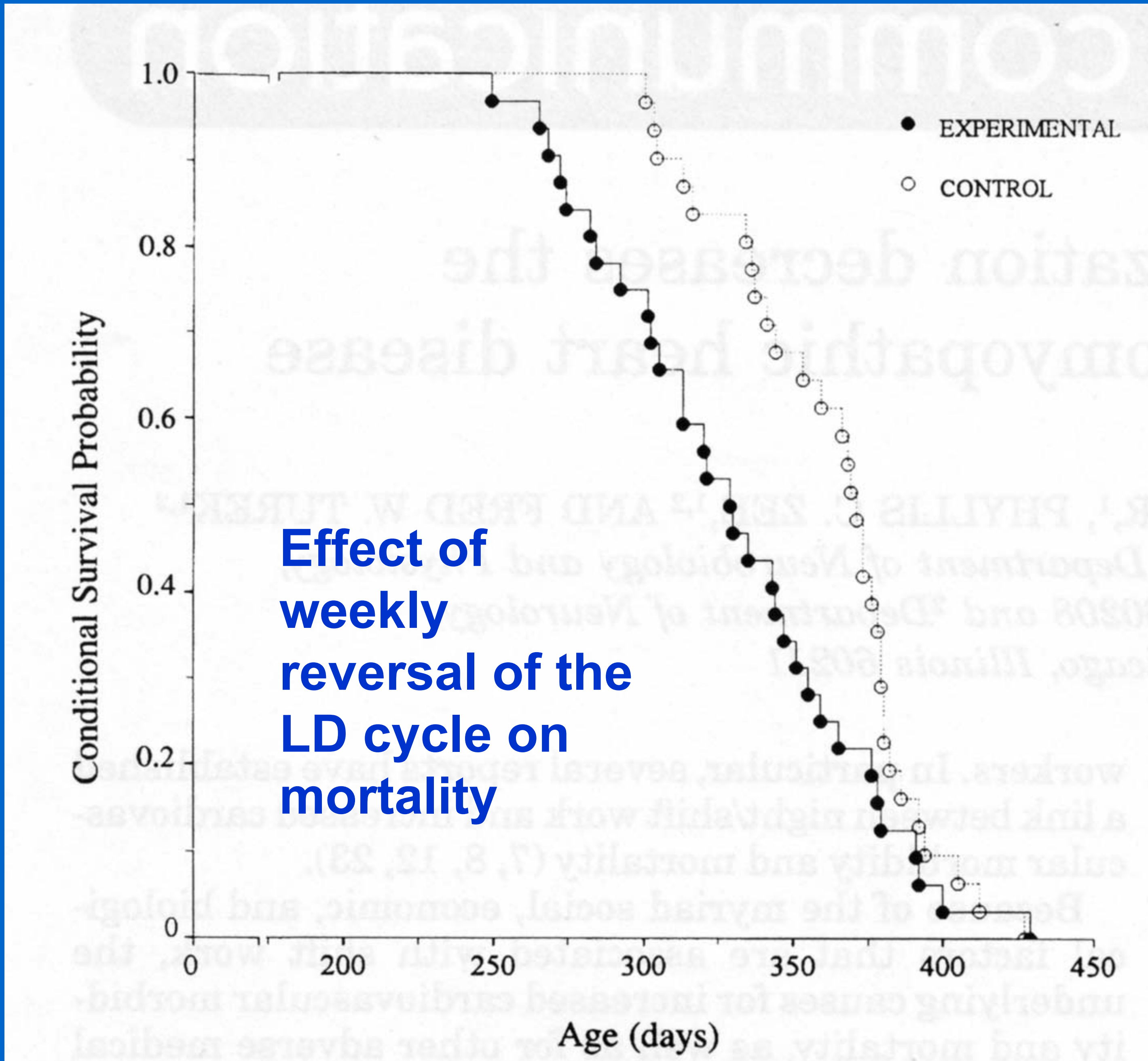
Substitute circadian dysregulation for insufficient Sleep



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 !!

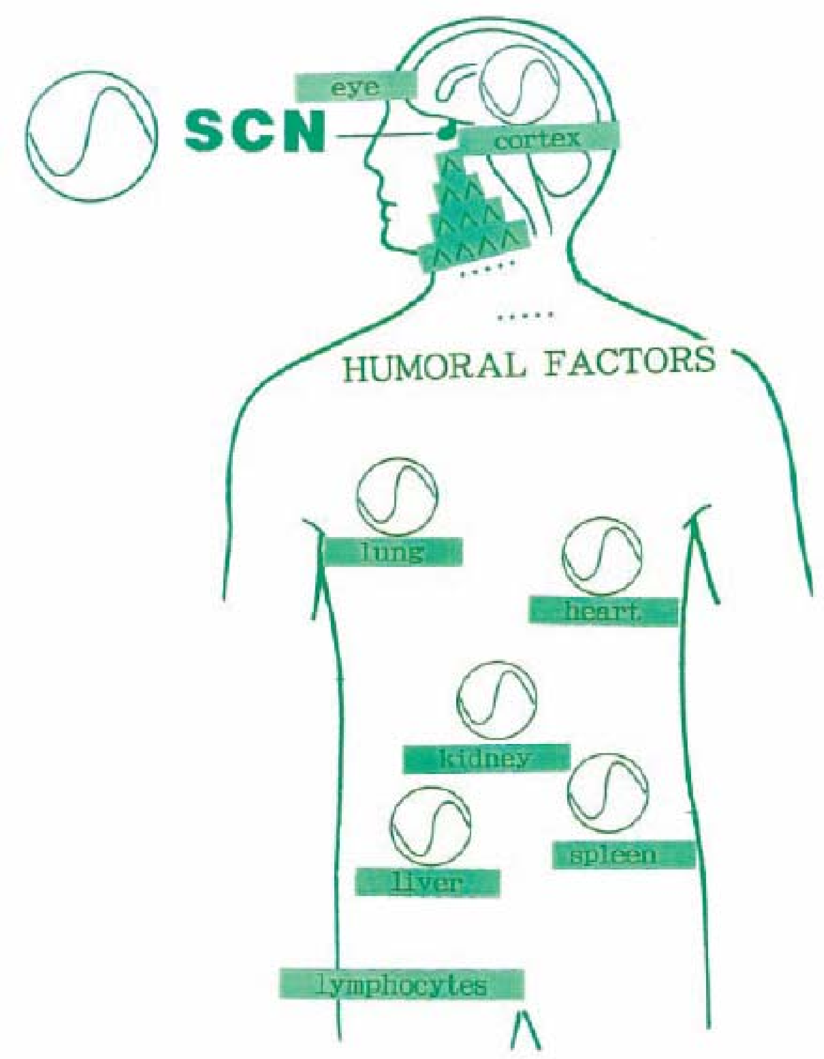


FIG. 2. The master clock (SCN) governs the peripheral tissue rhythm in mammals. The fact that the rhythmic expression of RPER2 mRNA in several tissues completely depends on the SCN suggests that some signals (Humoral Factors) are needed to maintain coordinately the rhythm of the whole body.

Ishida, Kaneko and Allada (1999)
PNAS, 96: 8819-8820

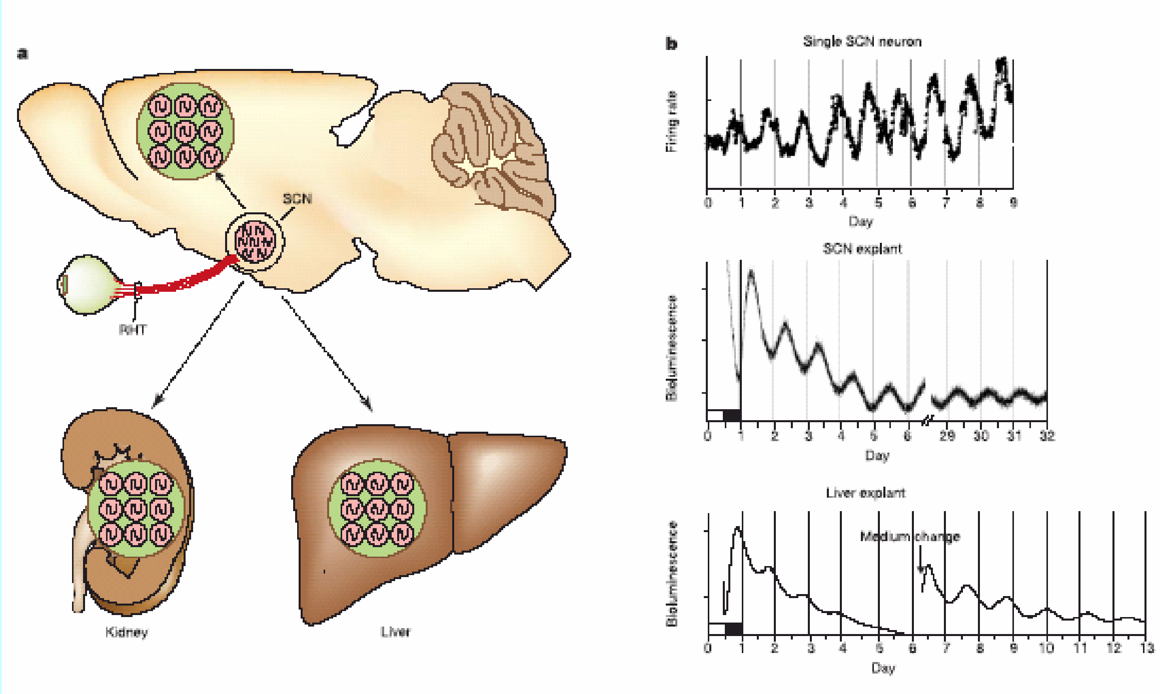
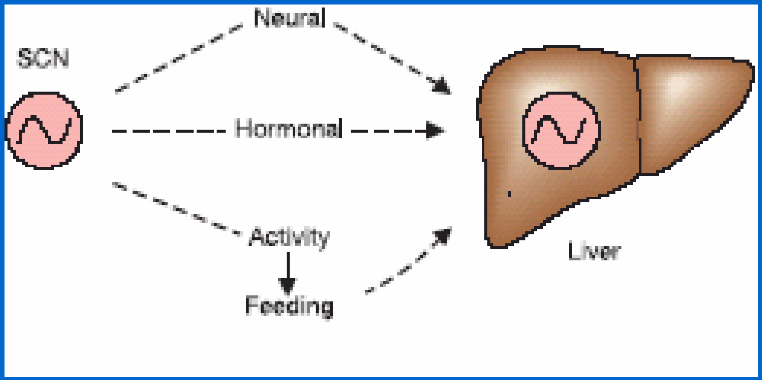
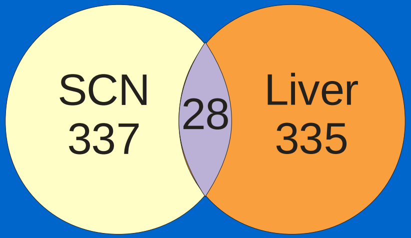


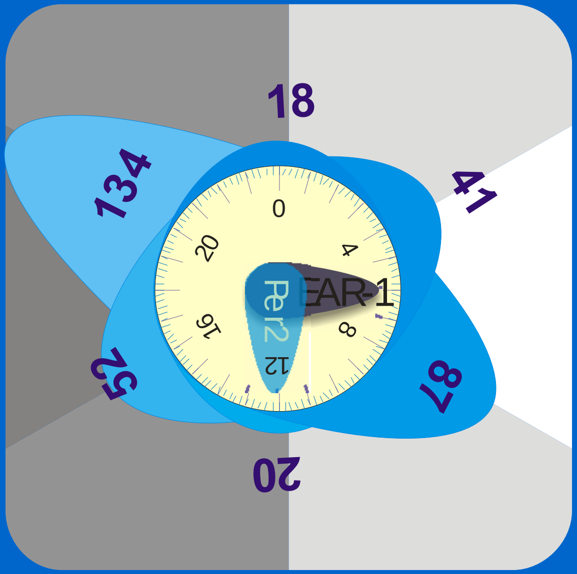
Figure 1 The mammalian circadian timing system is a hierarchy of dispersed oscillators. **a**, The master clock in the SCN is composed of numerous clock cells. The SCN receives light information by a direct retinohypothalamic tract (RHT) to entrain the clock to the 24-h day. The entrained SCN, in turn, 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 *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.

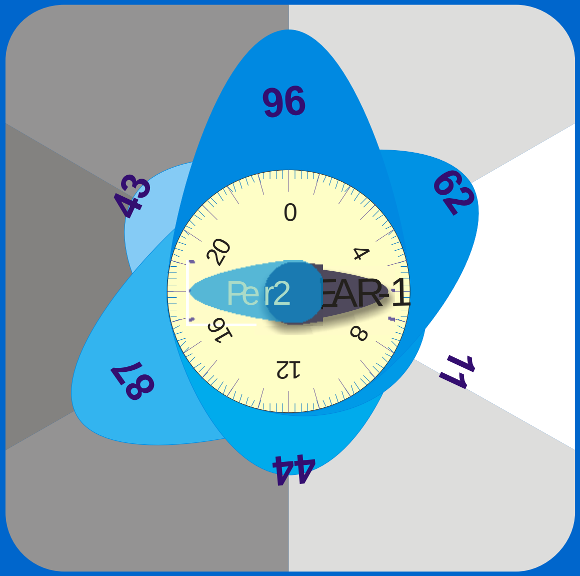


From:
Reppert and Weaver (2002). Nature (418): 935

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

Regulation of sleep-wake cycle

Brain Tissue Specific – Circadian Gene Dysregulation

NEW FRONTIER

Human Mental & Physical Health at Many Levels

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Sue Losee-Olson
Ketema Paul
Jonathan Shelton
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