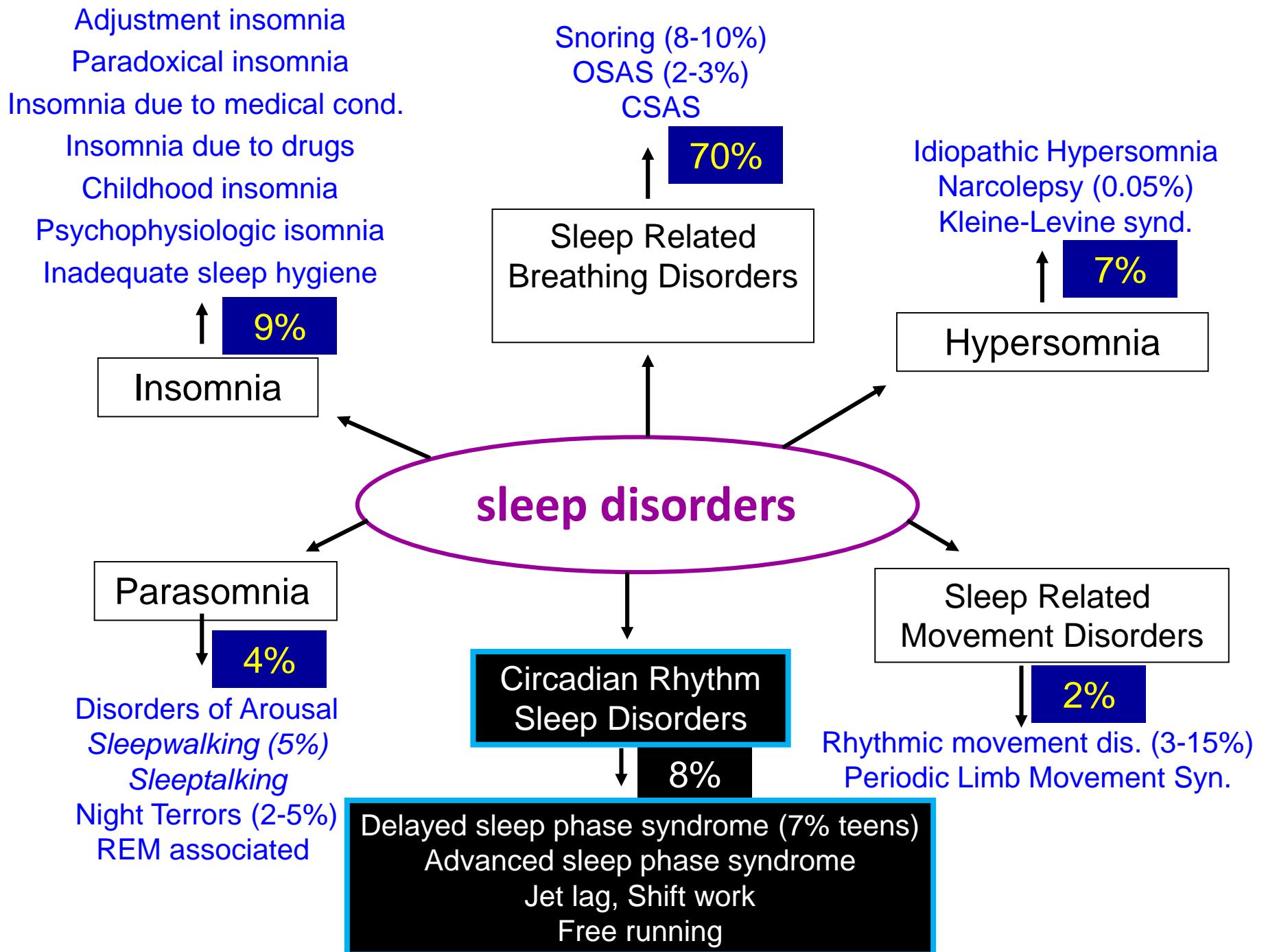


# כשהשעון הביולוגי מזייף

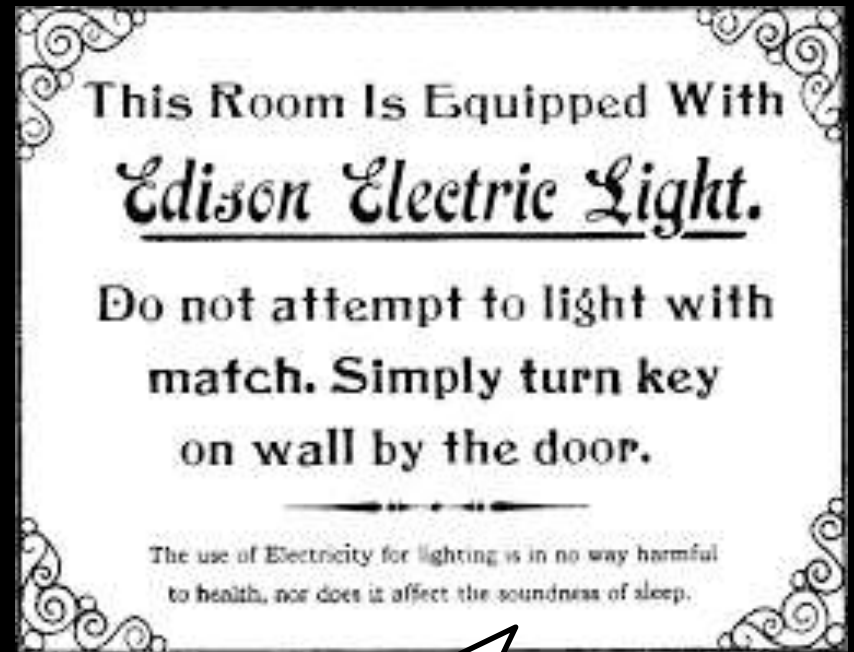
יעקב סיון

מכון ריאות, בי"ח "ספרא" לילדים, המרכז הרפואי שיבא



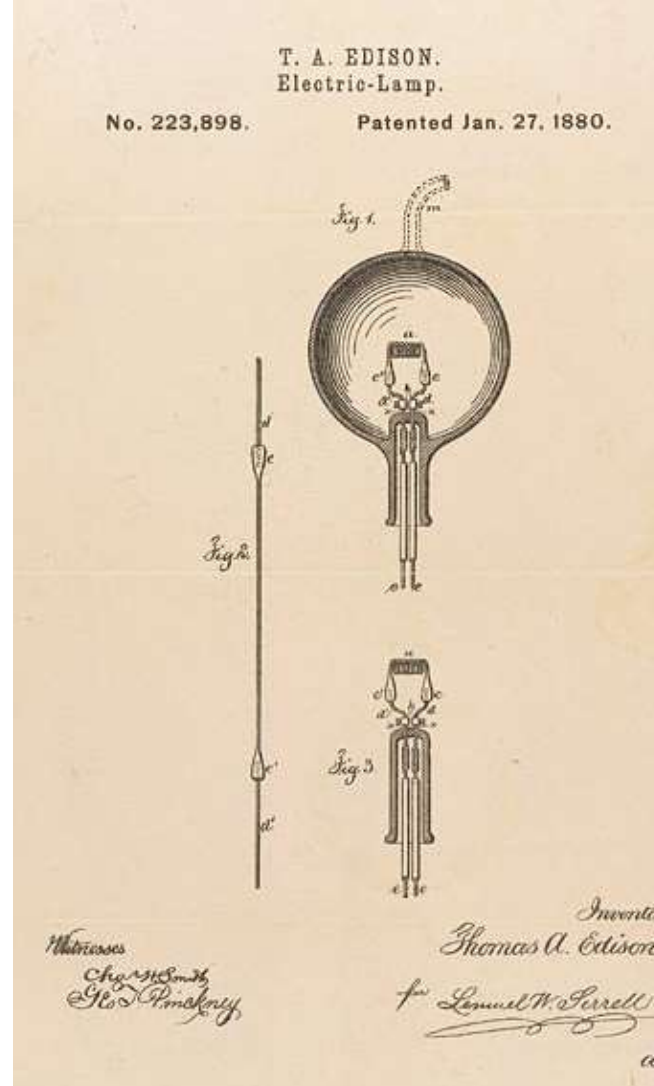
## Average hours of night sleep by country - adults

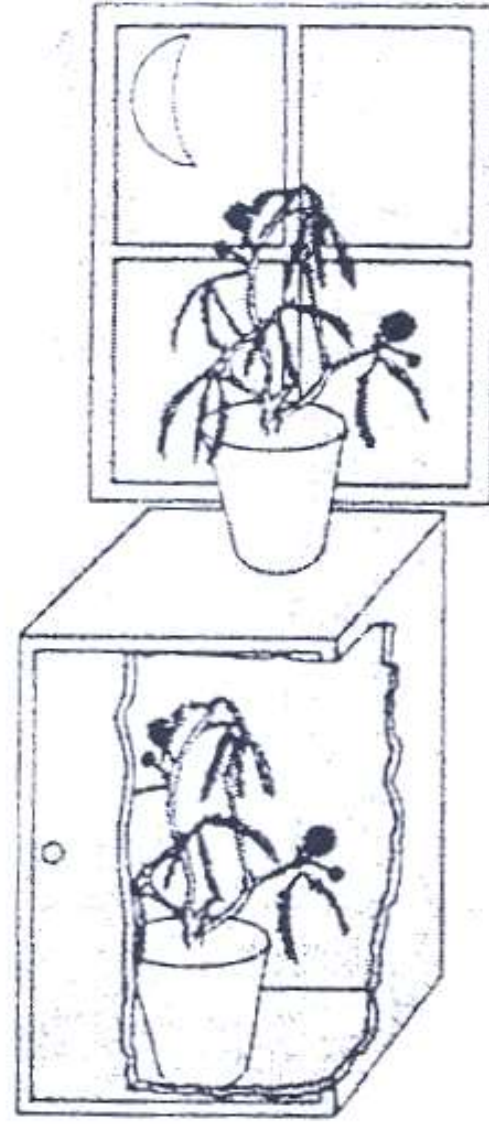
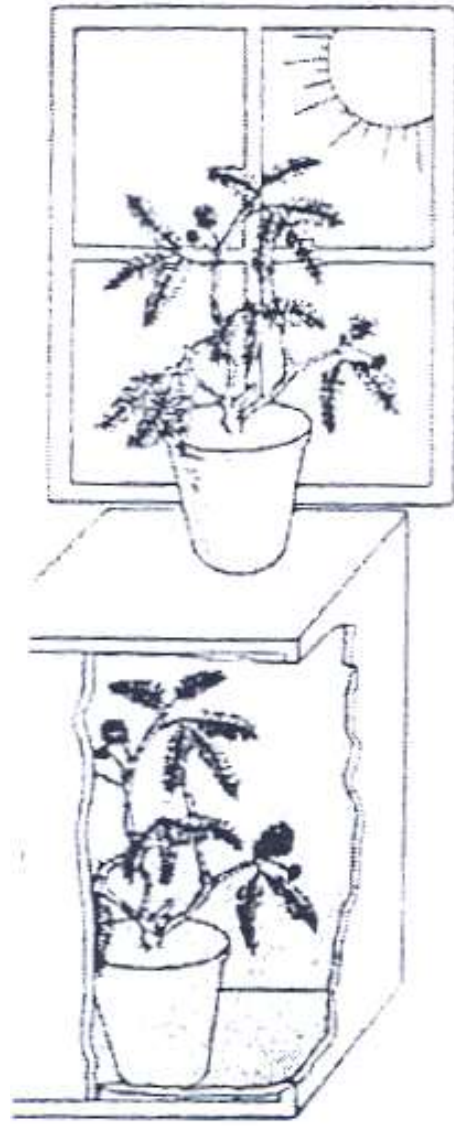
<b>France</b>	<b>8:24</b>
<b>Finland</b>	<b>8:12</b>
<b>UK</b>	<b>8:11</b>
<b>Hungary</b>	<b>8:08</b>
<b>Belgium</b>	<b>8.01</b>
<b>Denmark</b>	<b>8:00</b>
<b>Estonia</b>	<b>7:52</b>
<b>USA</b>	<b>7:00</b>
<b>Israel</b>	<b>6:30</b>



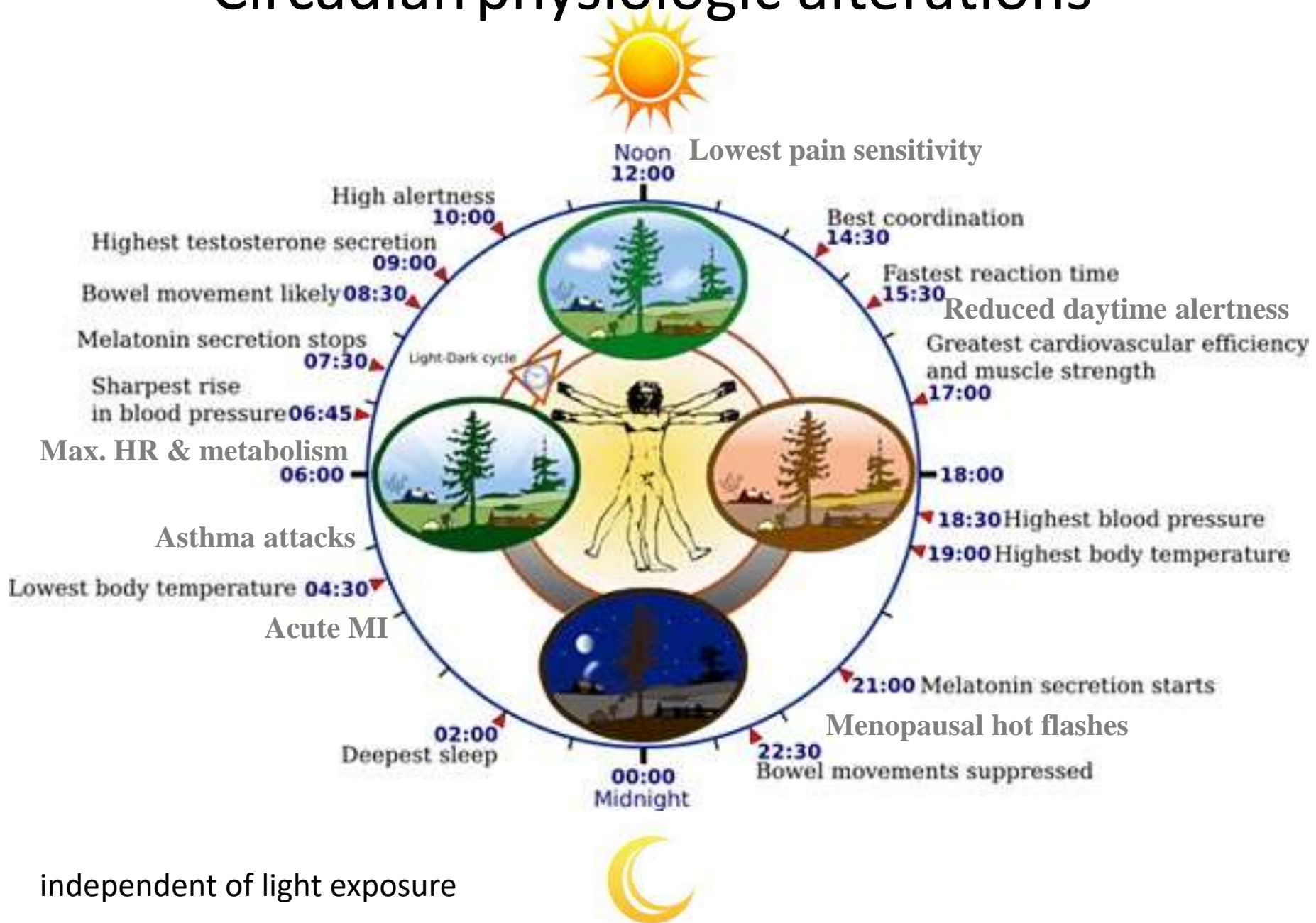
The use of Electricity for lighting is in no way harmful to health, nor does it affect soundness of sleep.

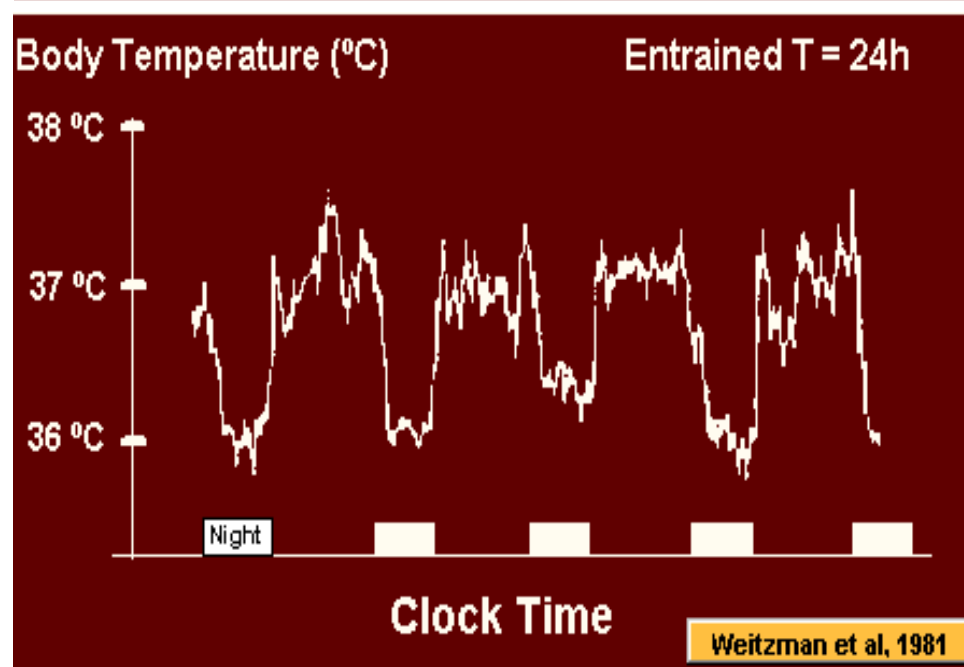
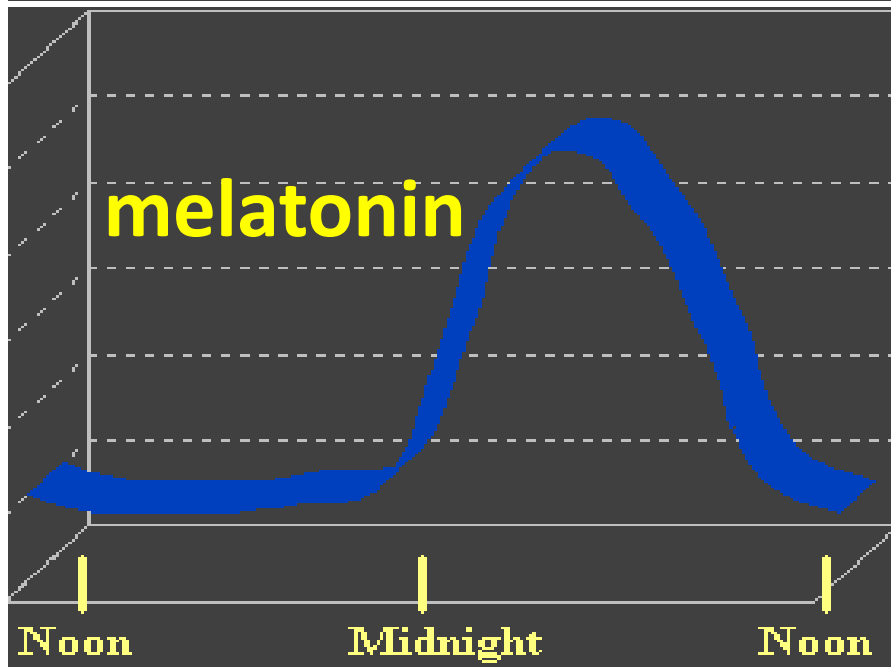
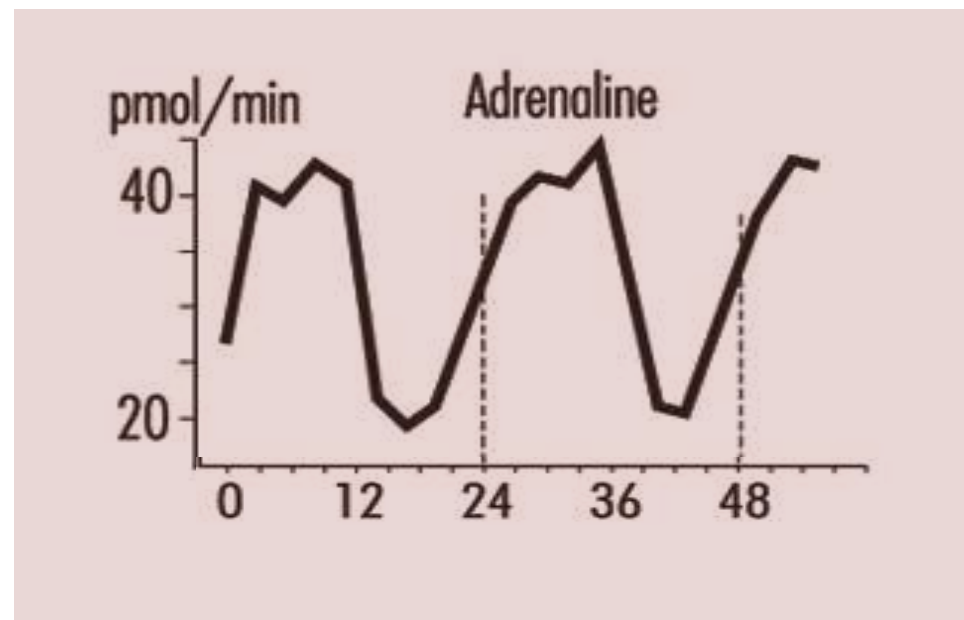
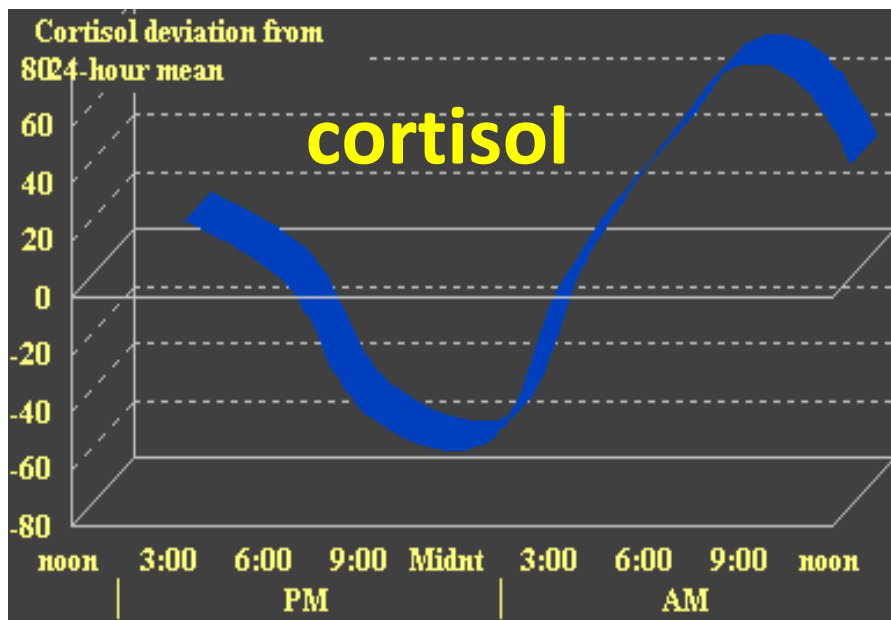
# The 1879 revolution





# Circadian physiologic alterations





The sleep-wake pattern has only a minimal effect on pattern of secretion



Cell, Vol. 63, 1257–1266, December 21, 1990, Copyright © 1990 by Cell Press

# **Expression of the Liver-Enriched Transcriptional Activator Protein DBP Follows a Stringent Circadian Rhythm**

**Jérôme Wuarin and Ueli Schibler**

Department of Molecular Biology

University of Geneva

30 Quai Ernest Ansermet

1211 Geneva-4

Switzerland

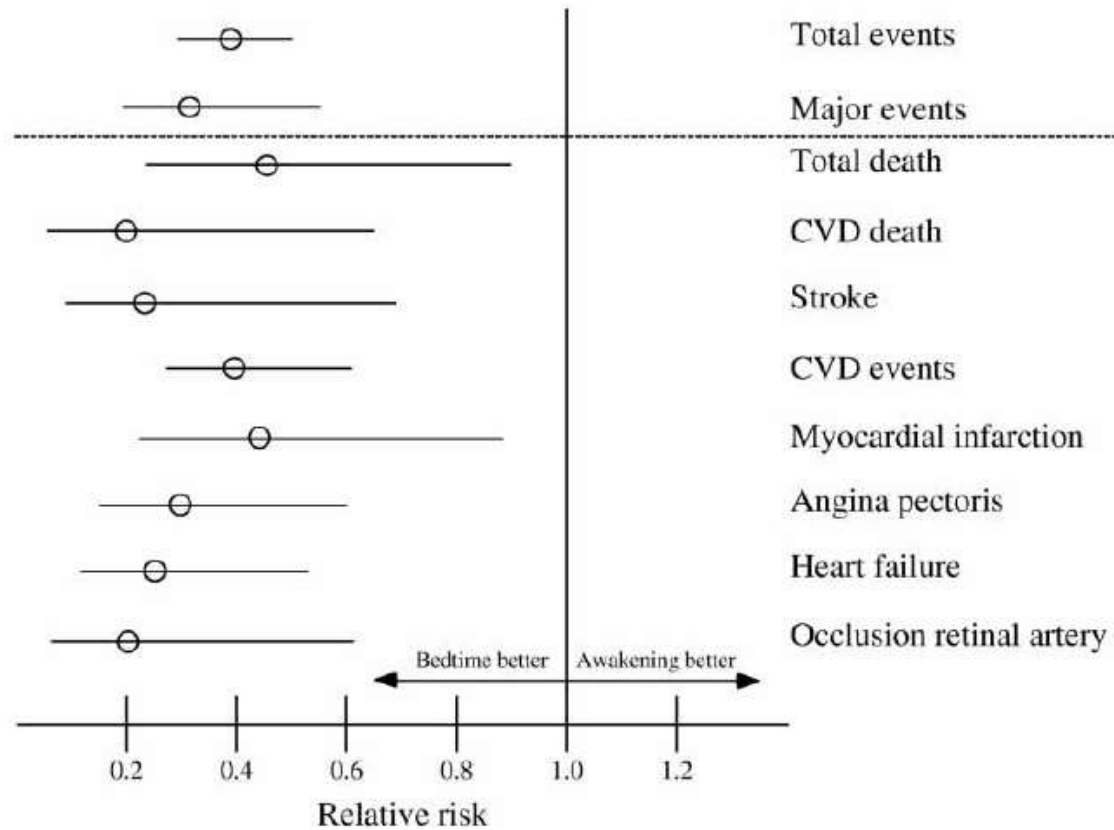
Chronotherapy – adjustment of meds to the activity of metabolizing or activating enzymes

# INFLUENCE OF CIRCADIAN TIME OF HYPERTENSION TREATMENT ON CARDIOVASCULAR RISK: RESULTS OF THE MAPEC STUDY

Ramón C. Hermida, Diana E. Ayala, Artemio Mojón & José R. Fernández

*Chronobiology International 2010*

Bedtime chronotherapy for hypertension reduces  
cardiovascular risk compared to conventional therapy



Relative risks (with 95% confidence intervals) of CVD events (adjusted by age, sex, and diabetes) as a function of time-of-day of hypertension treatment

# The circadian rhythm is independent of light (“self sustained”)

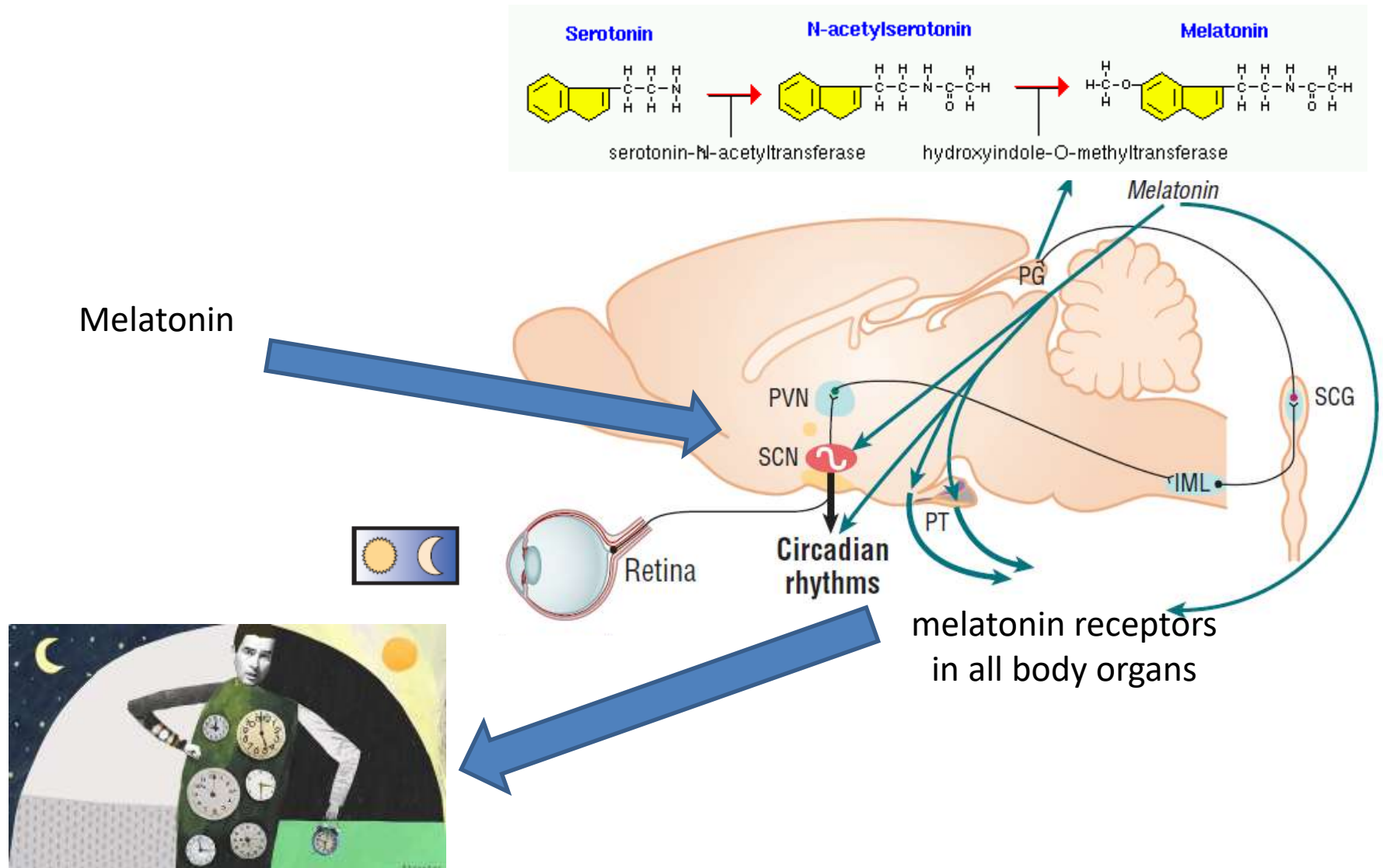
למרות ניתוק מהאור והחושך החיצוניים – המחזוריות הצירקדית



# Biological clock – endogenous pacemaker – master clock

## Biological clock - suprachiasmatic nucleus (anterior hypothalamus, 1972)

Hypothalamus, destruction causes loss of many CRs including sleep-wake.



# Biological master clock - synchronization

## Entrainment, synchronizers:

~ 24 h. +

- Morning light
- Noise
- Food, meals time
- Daily activity, social interactions
- Specific stimuli
- Temperature: phase shift but not circadian change (temperature compensation)

# Peripheral clocks

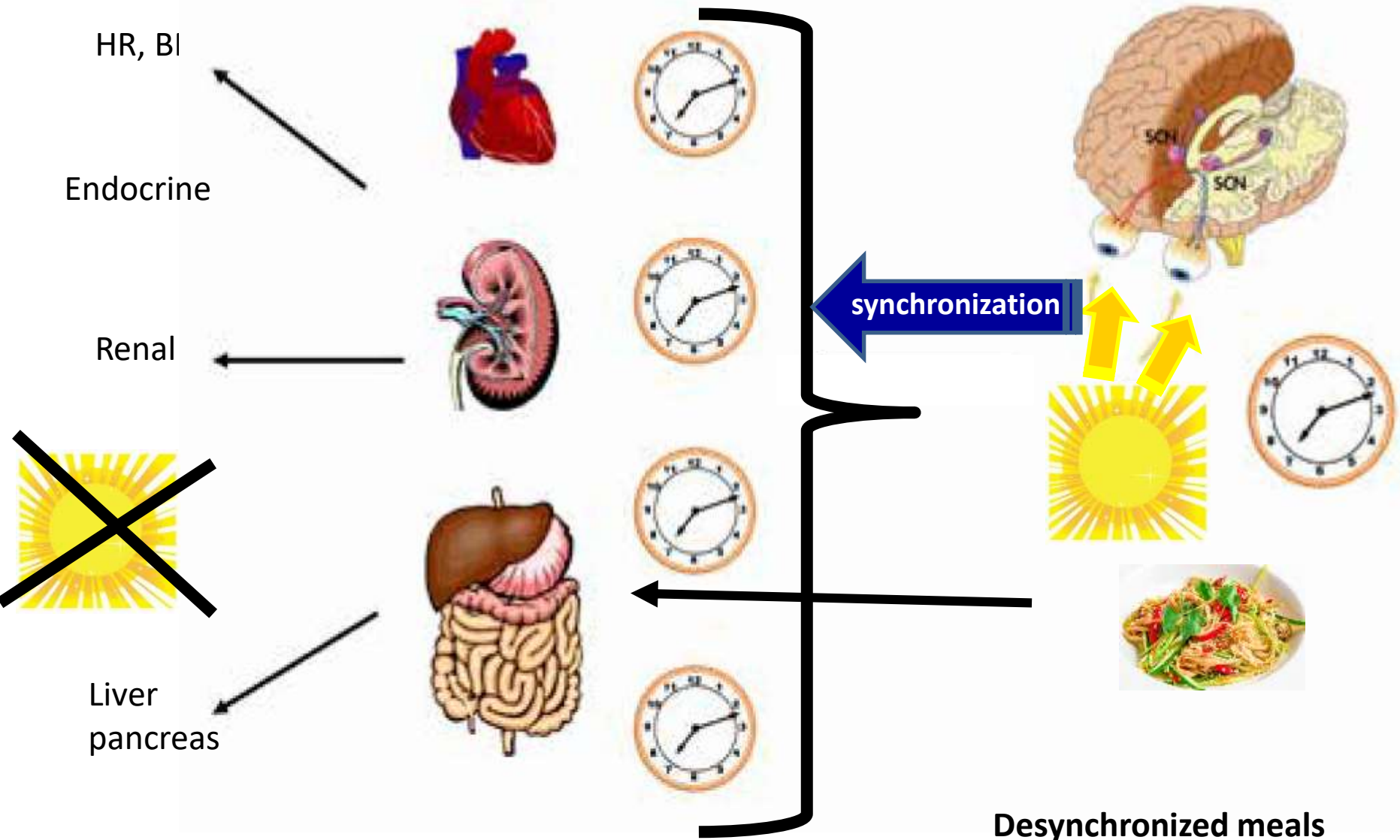
~ 24 h. – not synchronized by light

synchronization

same machinery

# central master clock

~ 24 h.



circadian desynchrony at the cellular, tissue, and behavioral levels may play much more widespread roles in human medical and psychiatric pathologies.

10-20% of the human (and animals) genes display circadian behavior.

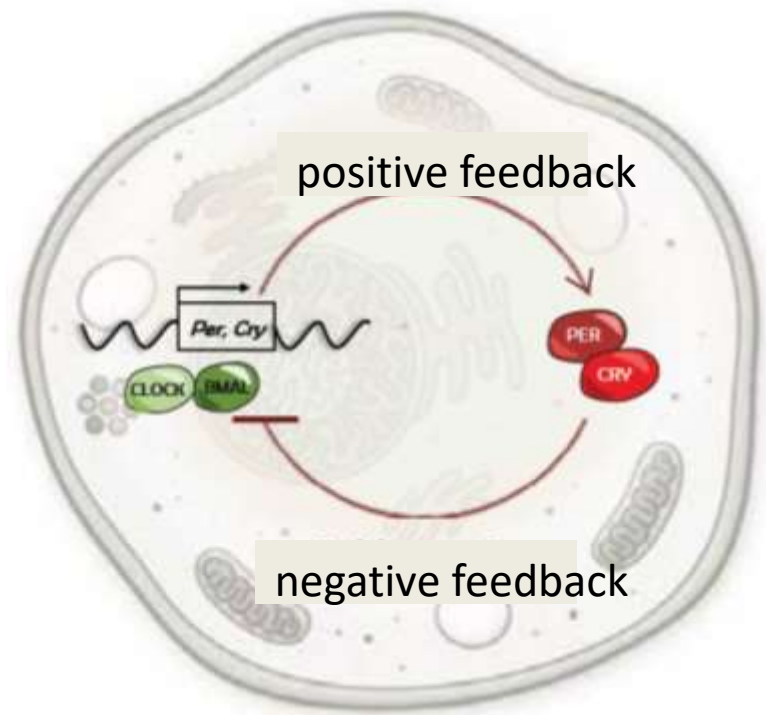
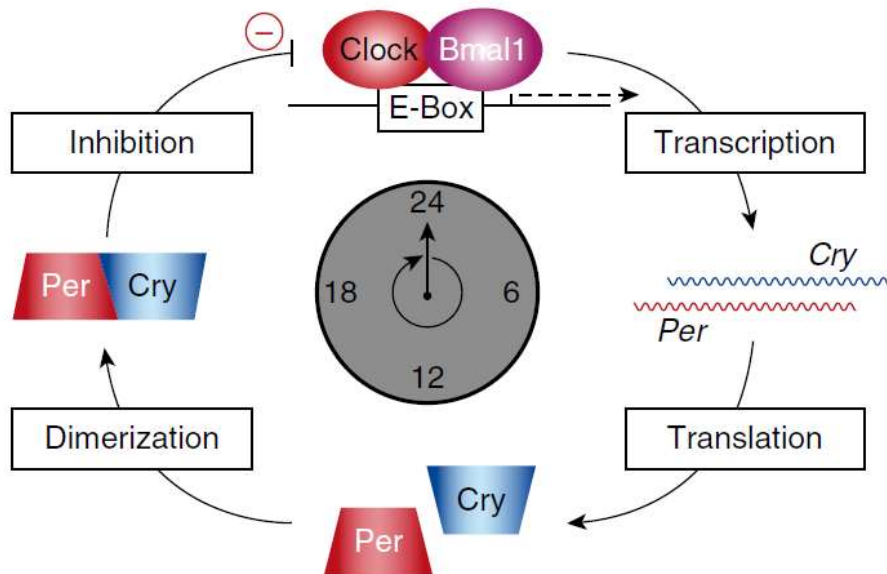
Hence, protein, enzymes (and lipids) levels show circadian levels.

Examples: **insulin, leptin, ghrelin, adiponectin, CS, glucose, TG, cholesterol, HDL**

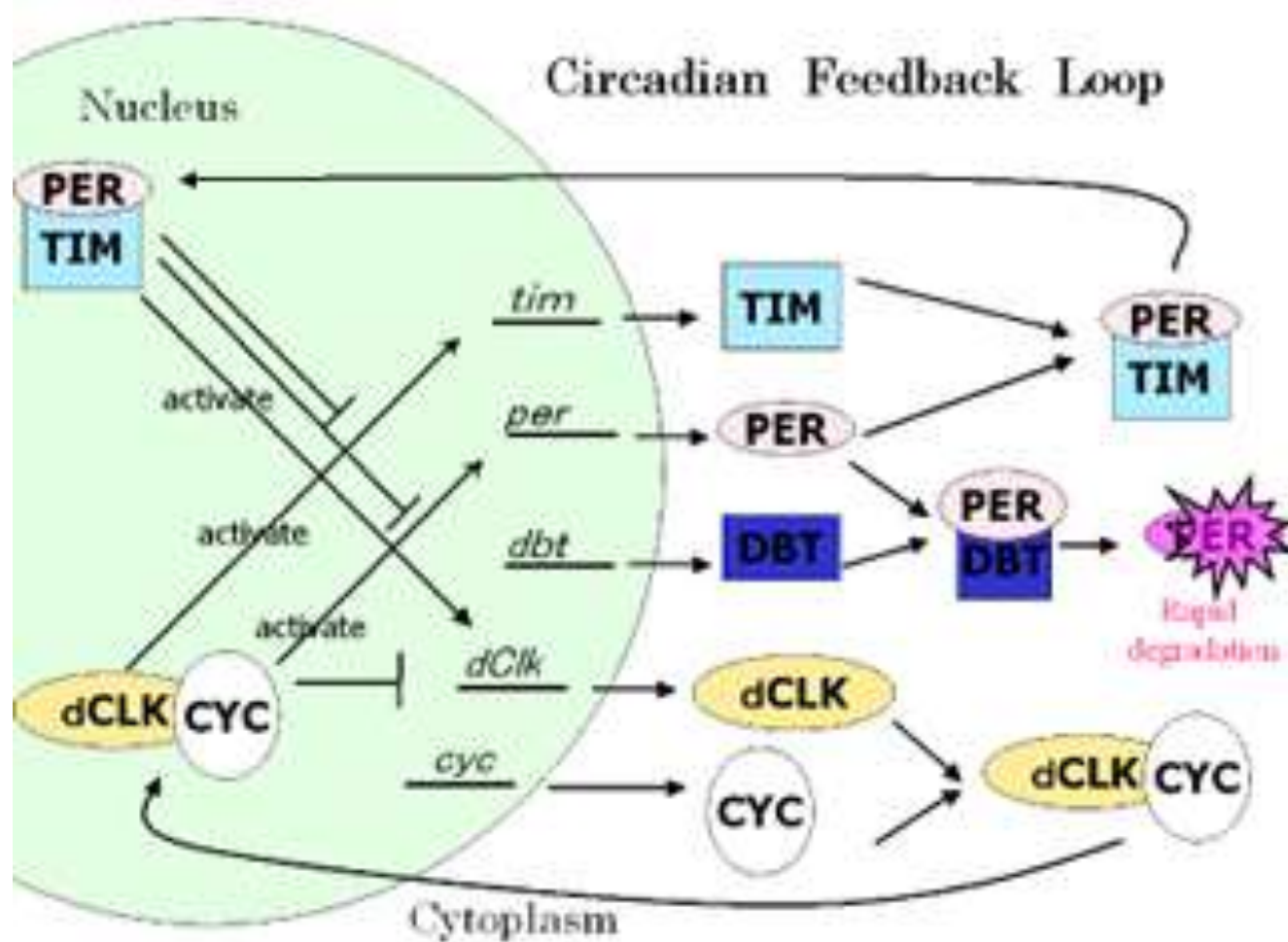


This molecular circadian clock machinery exists and can produce circadian rhythms in most or all body cells.

Transcription-translation loop  
Takes +24h.

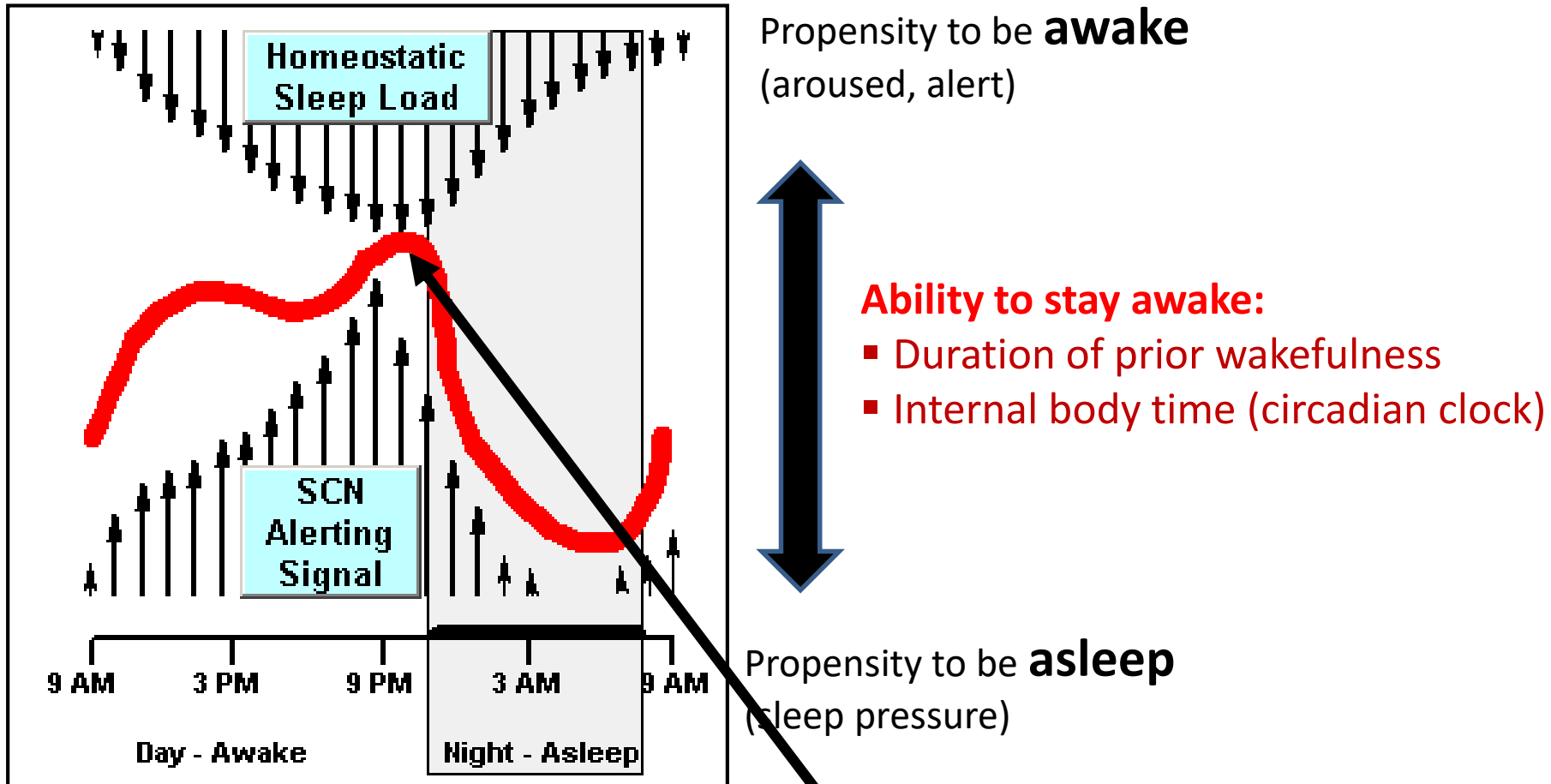


## Circadian Feedback Loop



# Sleep homeostasis

Sleep homeostat – accumulation and dissipation of sleep pressure  
(adenosine = neuromodulator)



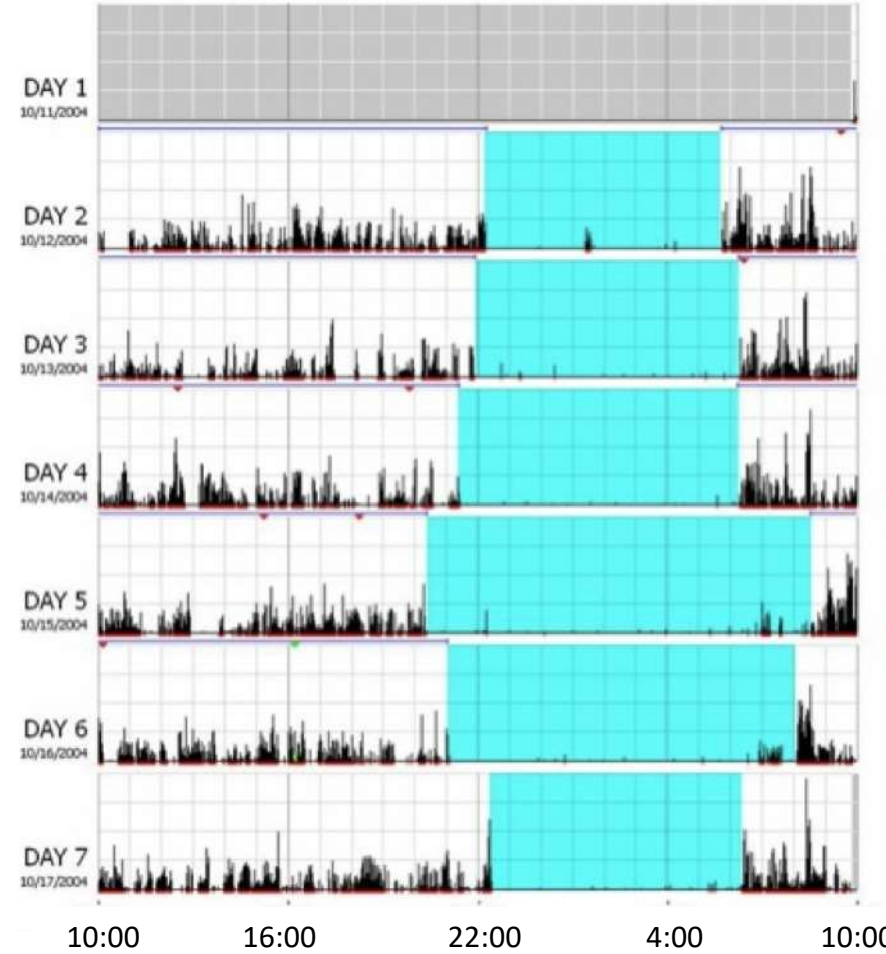
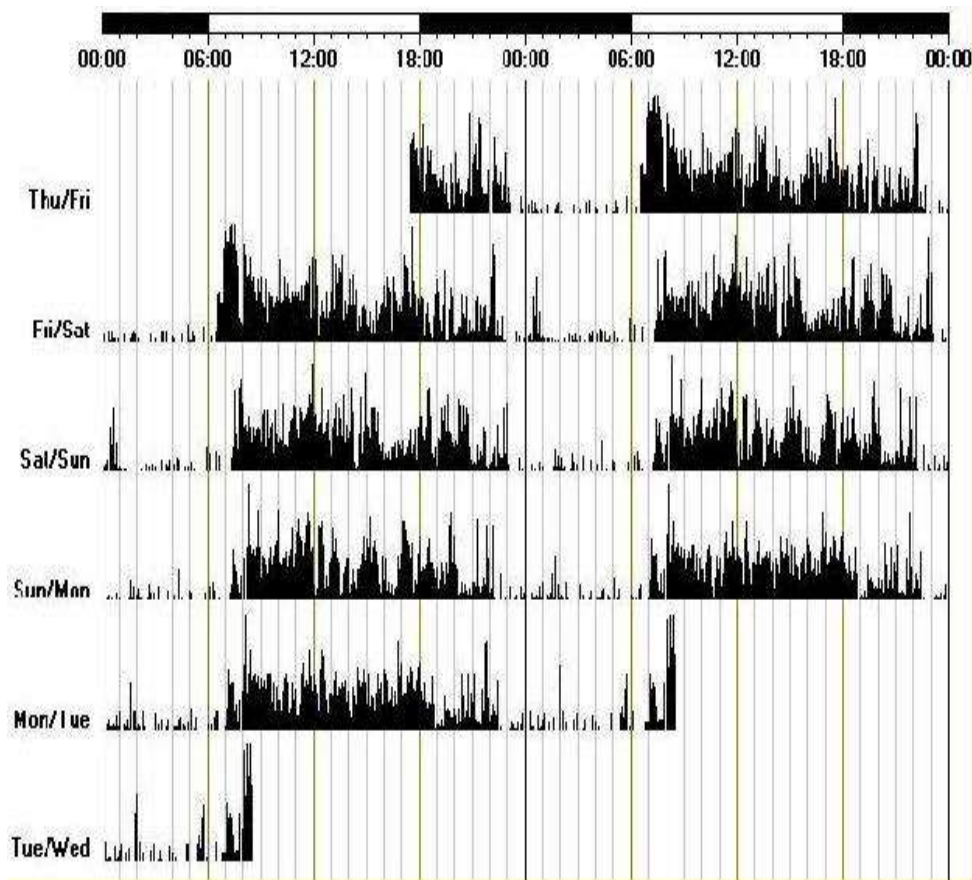
Circadian cycle/clock – regulates the daily arousal / sleep propensity.

Arousal **increases** throughout the day, maximal – immediately before plasma melatonin increase (circadian power overcomes accumulated asleep homeostatic load).

# Actigraphy

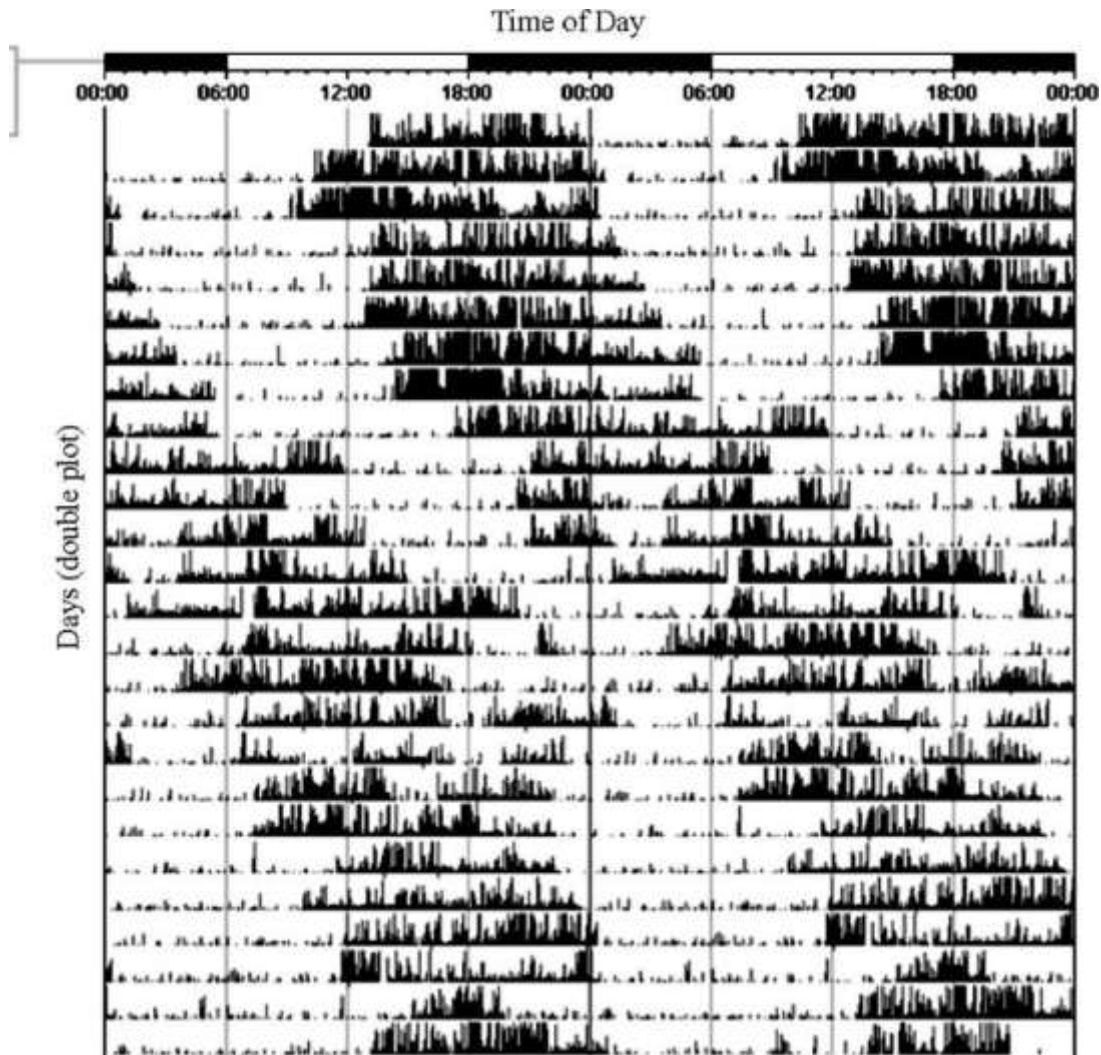


normal





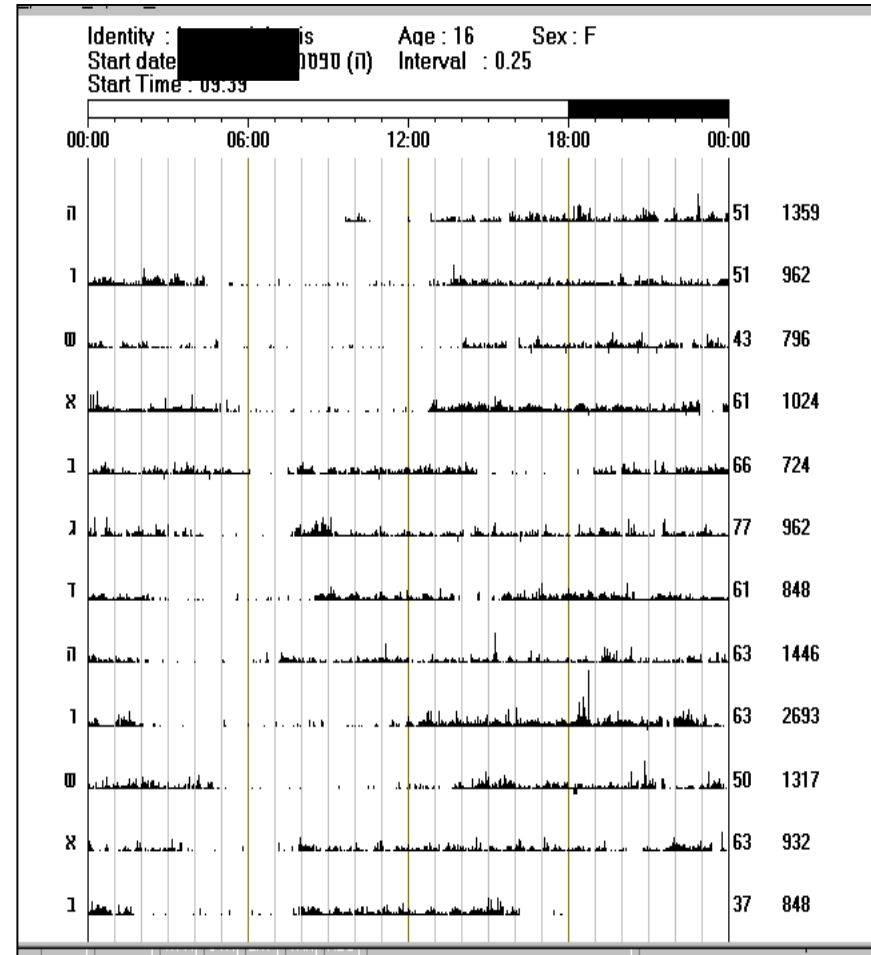
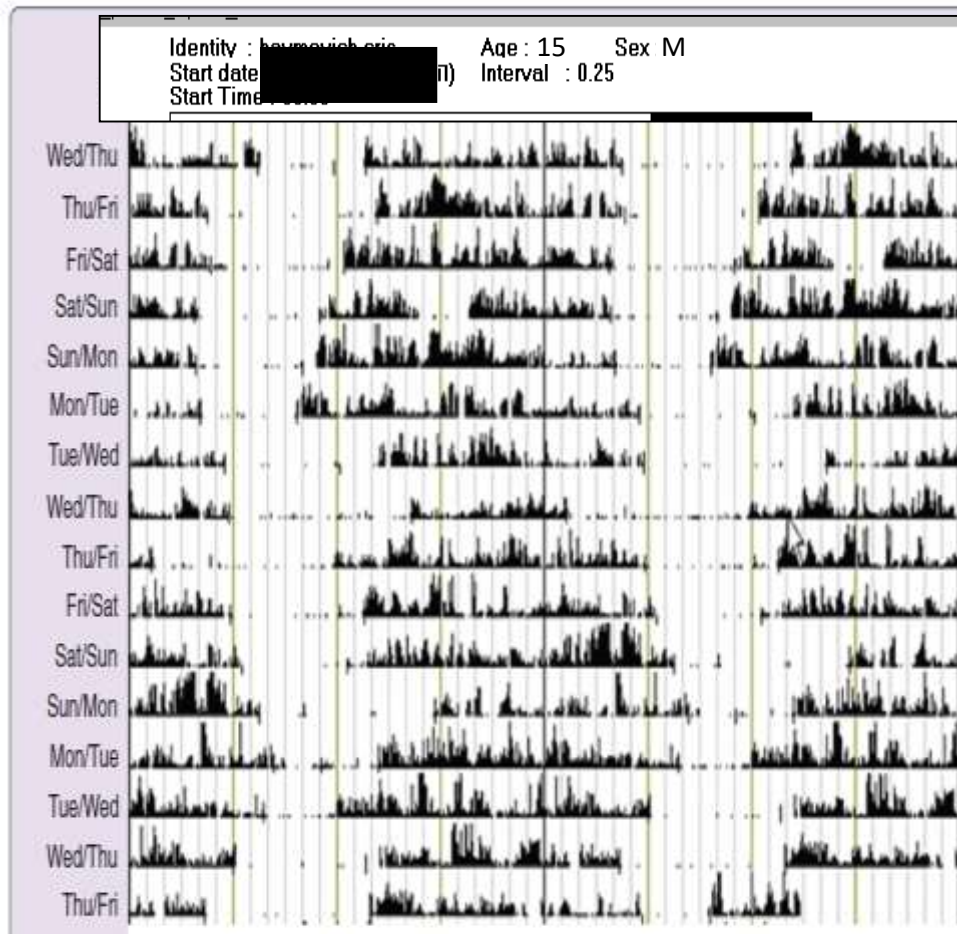
## Non-24 sleep-wake syn. (free runner)



# **Sleep disorders associated with circadian rhythm abnormalities**

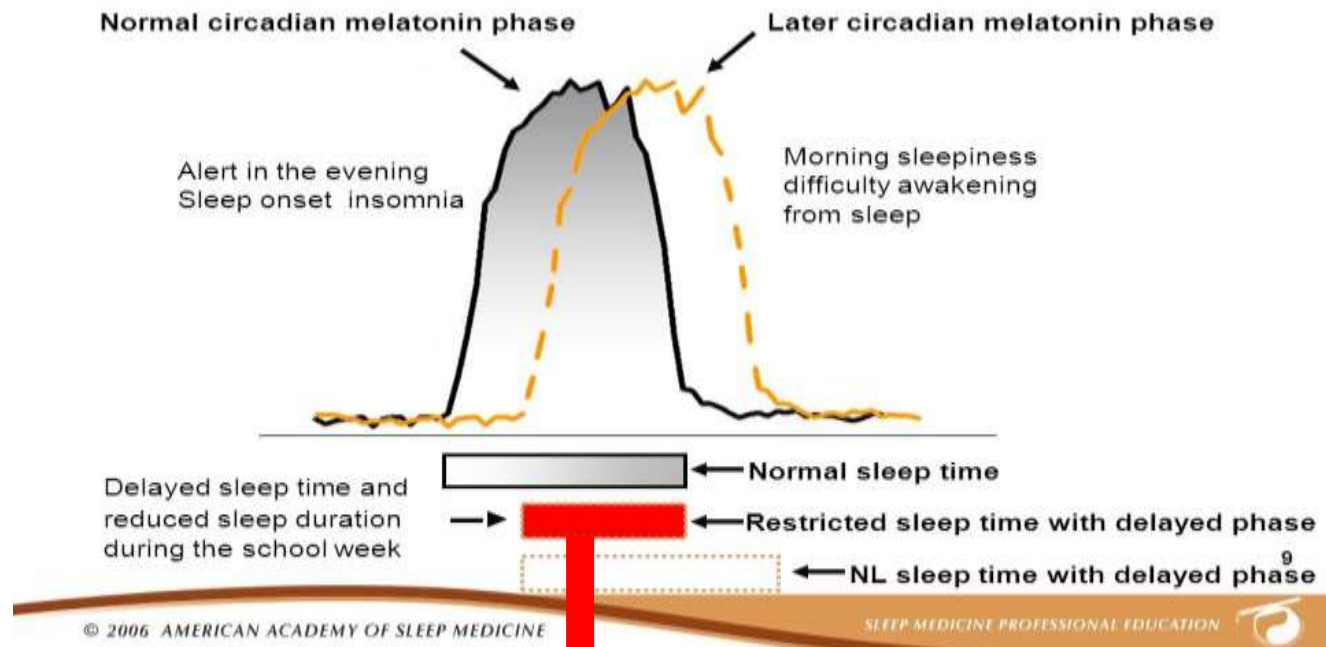
- Delayed sleep phase syndrome
- Advanced sleep phase syndrome
- Non-24 h. sleep-wake syndrome
- Jet lag
- Shift workers
- Blind individuals
- Irregular sleep-wake pattern
- Aging

# Delayed Sleep Phase Syndrome, DSPS

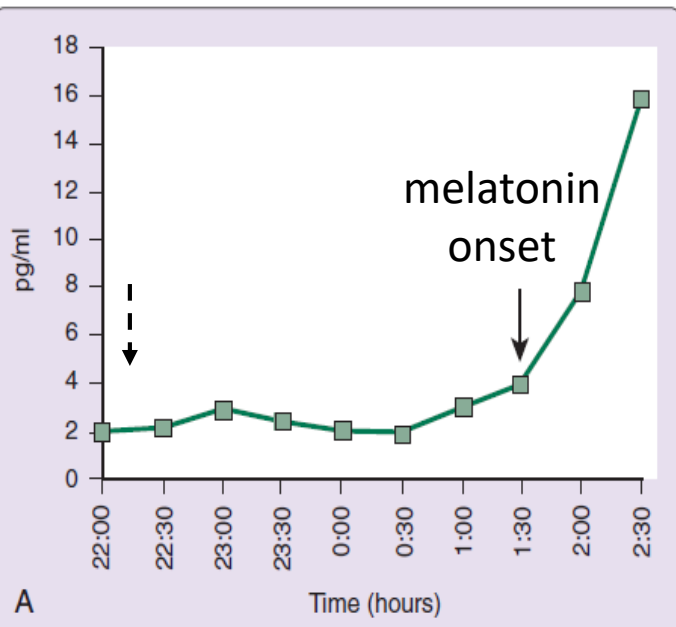


- sleep onset and wake times that are usually delayed 3 to 6 hours.
- most alert in the late evening -night people.
- 7% in adolescents and young adults.





Enforced “conventional” wake times result in chronically insufficient sleep and excessive daytime sleepiness.



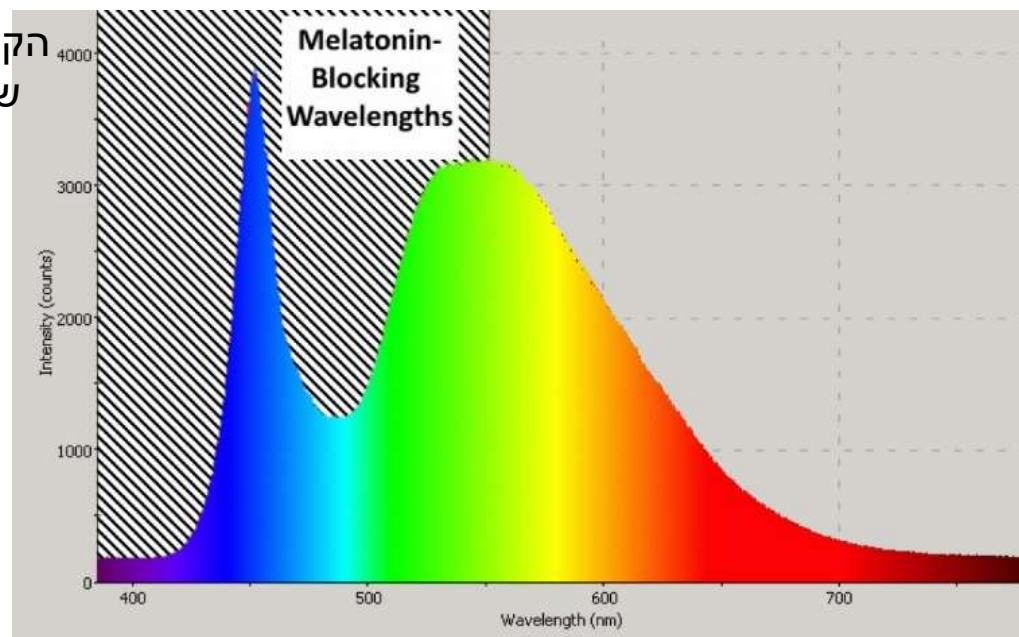
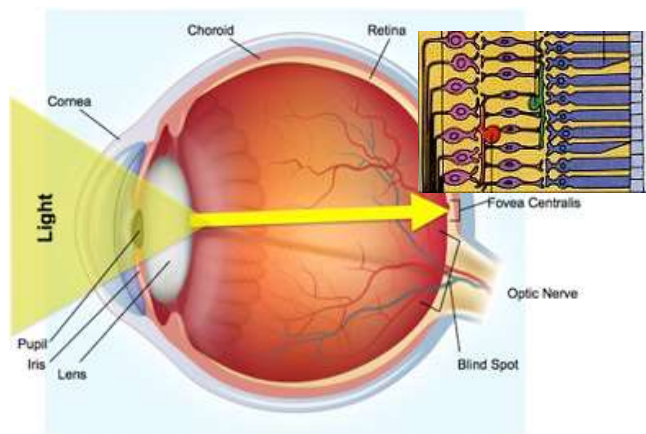
# Delayed Sleep Phase Syndrome - Pathophysiology

- **Genetic** – autosomal dominant, polymorphism in circadian genes.
- **Behavioral induced** – late activities, evening exposure to light, late wake-up and late exposure to morning entrainment.

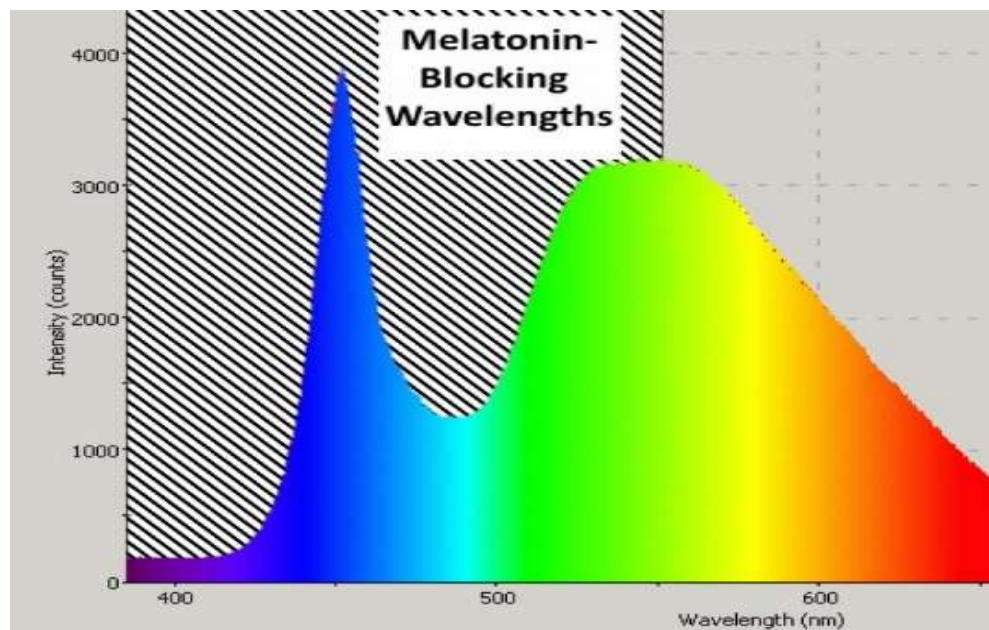
*"All illnesses have some hereditary contribution. Genetics loads the gun and environment pulls the trigger"*

*(Francis Collins ,Director, National Human Genome Research Institute)*

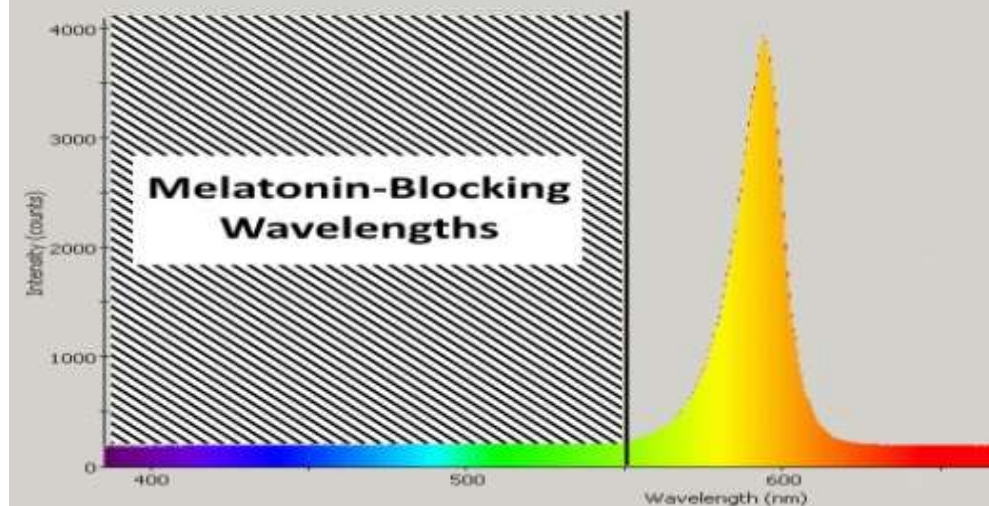
הקולטן לאור ברשתית שנקרא מלנופסין – רגיש לתחום צר של האור הכחול (460-480 nm) שמדכא יצירת מלטונין



LCD computer and phone screens emit a higher percentage of melatonin-blocking blue wavelengths than most light bulbs. Light from electronic screens decreases melatonin levels may cause insomnia and daytime sleepiness.



**Spectrographic Analysis of a native Amber LED  
(Provided by LEDMuseum.candlepower.us)**



400 450 500 550 600 650 700

**Wavelength (nm)**

← Visible Spectrum →

Many people **cannot switch to amber lights** at night, because they work a night shift or spend their evenings on a computer.

**Blue-blocking glasses** filter out up to 99% of the blue wavelengths.

Late night computer users are able to fall asleep an average of **43 minutes earlier** when wearing blue blocking glasses.

# Delayed Sleep Phase Syndrome - Treatment

sleep  
hygiene +

+

+



+

Behavioral –  
sleep hygiene,  
avoidance of  
evening arousing  
activities and  
caffeine

Light –  
morning entrainment  
5,000 – 10,000 lux

Blue light  
restriction  
evening

Melatonin

**Treatment results in both wake-sleep time and physiologic changes (temp.)**

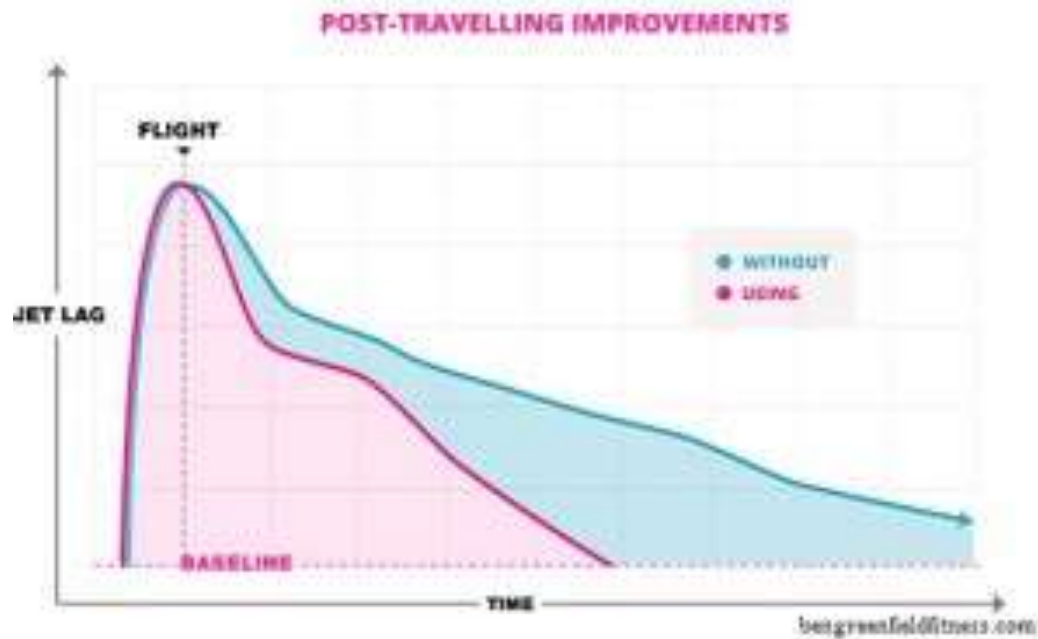
# Jet lag

- > 5 time zones
- Inability to sleep, premature awakening
- Inappropriate sleepiness

Adaptation to time zone at different rates:

- Asymmetry effect (east vs. west)
- age

# Gradual reentrainment – 2 h./day influenced by light intensity





# Jet Lag Treatment

Zolpidem (Ambien, Stilnox)  
before eastbound  
transatlantic nighttime  
flight and/or at bedtime in  
the new time zone

- ❑ Prevention treatment (light + early awakening + melatonin timing)

# **SHIFT-WORK SLEEP DISORDER**

10% of shift workers

## **Definition:**

Insomnia (after night shift) or excessive sleepiness (during night work) temporally associated with a work period that occurs during the habitual sleep phase.

Most night shift workers do not adapt:

- Light-dark cycle opposes their adaption
- Most night-shift workers revert to daytime wakefulness and nighttime sleep on days off
- Total sleep time decreases

# SHIFT-WORK SLEEP DISORDER

fall asleep – 34 min. faster

Sleep efficiency – 4.6% higher

Sleep fragmentation – 4.2% lower

- Cardiovascular morbidity
- Depression
- Type II diabetes
- Overweight / obesity / metabolic dysregulation
- Malignancy

לילה טוב

המשך כנס נעים

שינה טובה