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Circadian Rhythms and Insomnia

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Type of Potential Conflict	Details of Potential Conflict
Grant/Research Support	NONE
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Circadian Rhythms

- Understand the function of the suprachiasmatic nucleus (SCN)
- How much sleep do we need
 - It's only insomnia if there is loss of function
- Self induced insomnia
- Insomnia of childhood
 - Limit setting disorder
 - Sleep association disorder
- Understand common circadian rhythm disorders (CRDS)



Why Spend a Third of Our Lives Sleeping?



- Humans sleep nearly 8 hours/day, 56 hours/week, 224 hours/month and 2,688 hours/year.

How Much Sleep Do We Need?

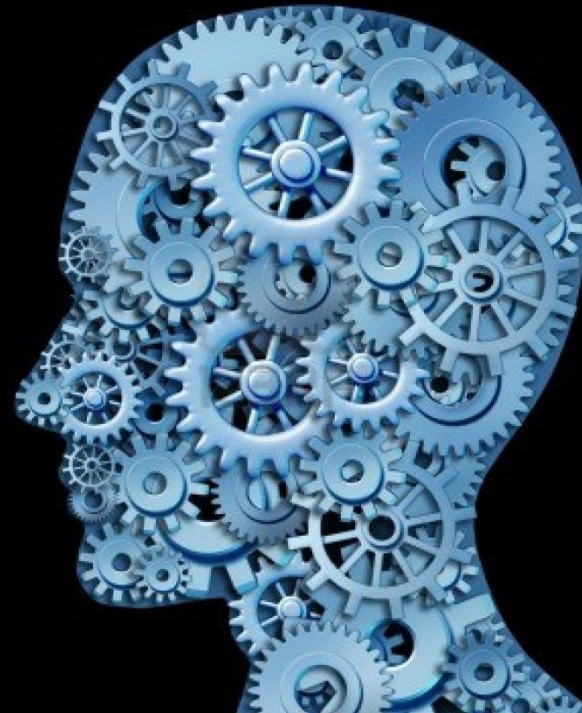
Age	Hours of sleep needed
0-3 mos	15-17
3-18 mos	13-15
18 mos – 3 yrs	11-13
4-12 yrs	10
Teens	8 ½- 9 ½
Adults	7-9



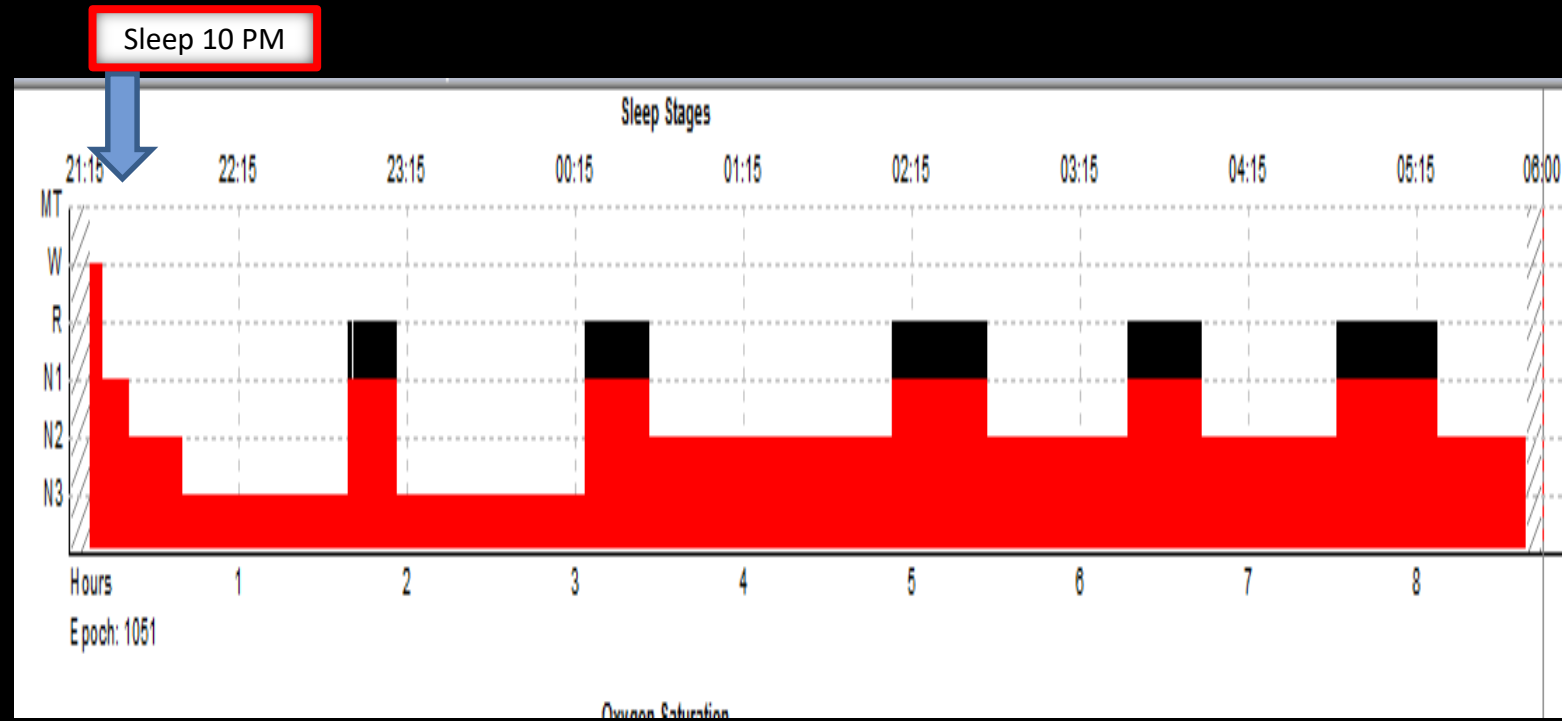
Source: National Sleep Foundation

Sleep is an Active Process!

- Memory and learning;
 - Sleep loss accelerates AD
- Immune function;
- Helps maintain ideal body weight
 - Ghrelin
 - Leptin
- Brain growth, development & repair;
 - Brain plasticity
- Maintaining normal body & hormone functions;
 - GH
 - Testosterone
- Growth & healing of tissues.



NORMAL SLEEP PATTERN

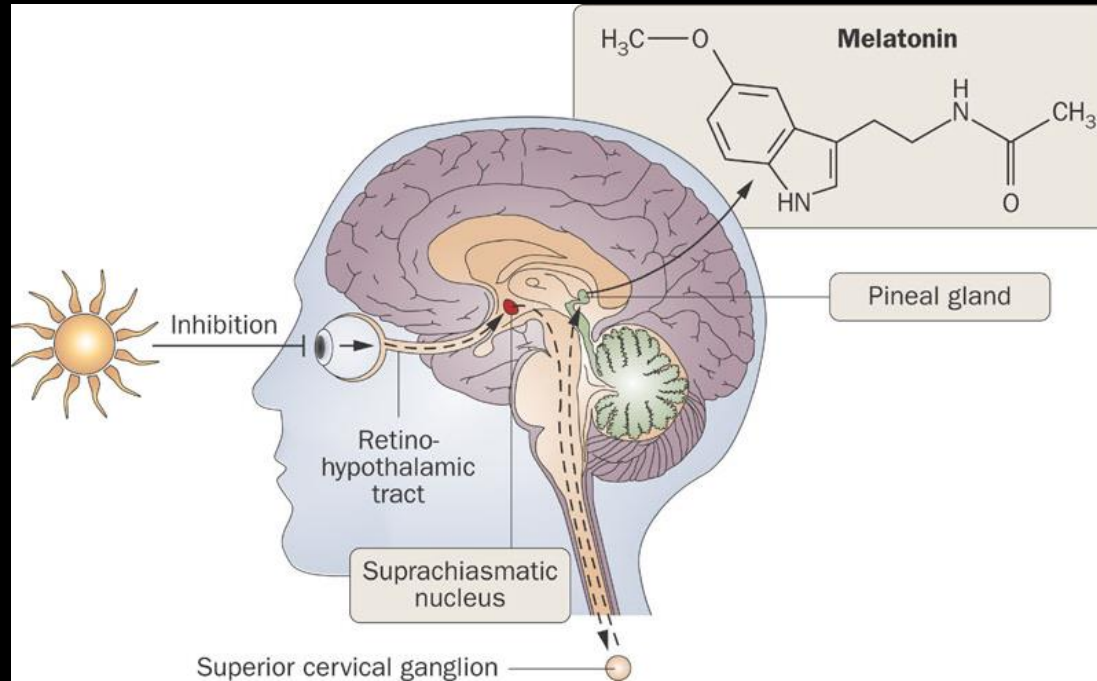


Meal 6 PM

Melatonin 8PM

Third Eye = Ajna Chakra = Pineal Gland

What is the “Timing System” that wakes us up and makes us sleep?



- Galen (2nd century) thought it a valve that regulated thought.
- Descartes believed it was the nexus between the mind and the body, the "seat of the human soul."

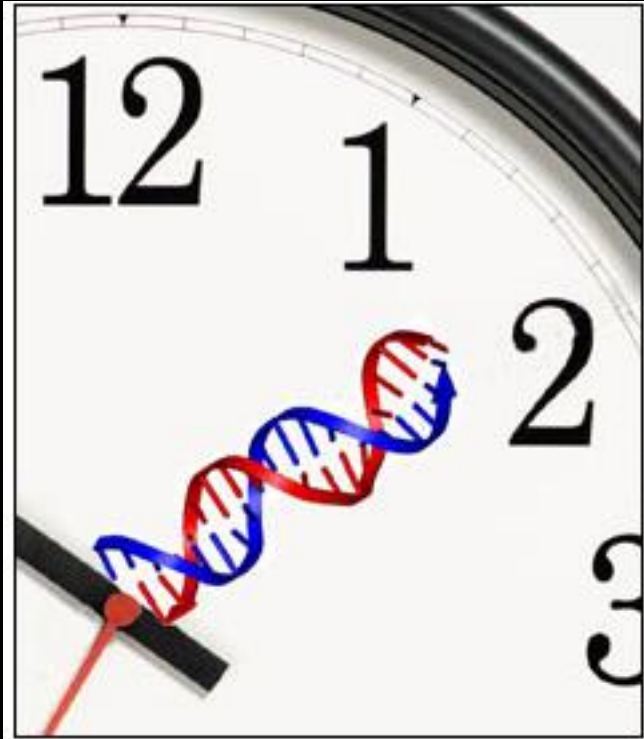


Suprachiasmatic Nucleus (SCN) Is Our Master Endogenous Pacemaker



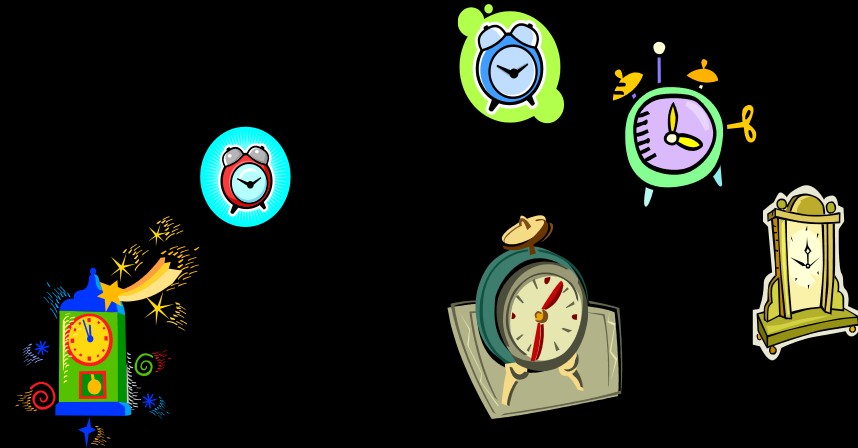
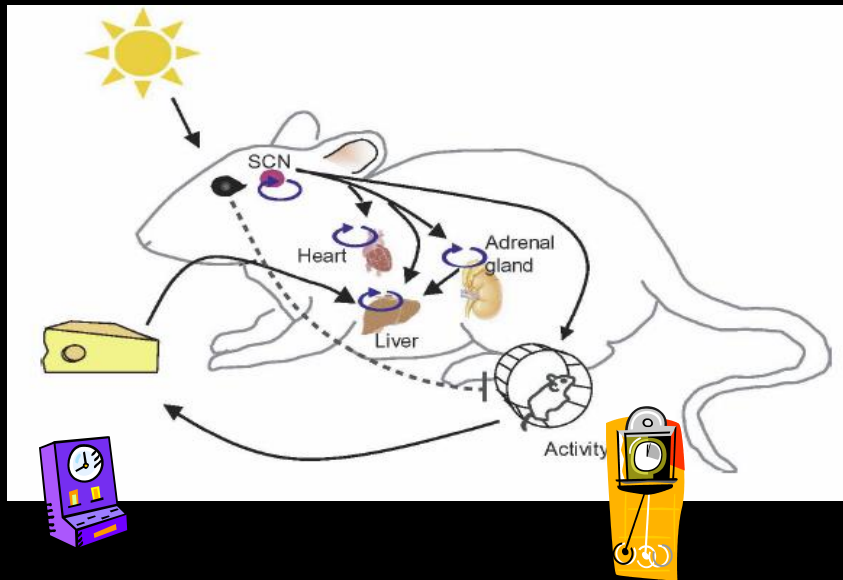
- SCN = a cluster of ~10,000 neurons located in the anterior (ventral) hypothalamus on either side of optic chiasm, ~3 cm behind the eyes.

Clock Genes



- Regulate the sleep wake cycle and have receptors throughout the body:
- Period I, Period II, Period III
- Cry I, Cry II

Circadian Clocks have been found in organs and peripheral tissues.



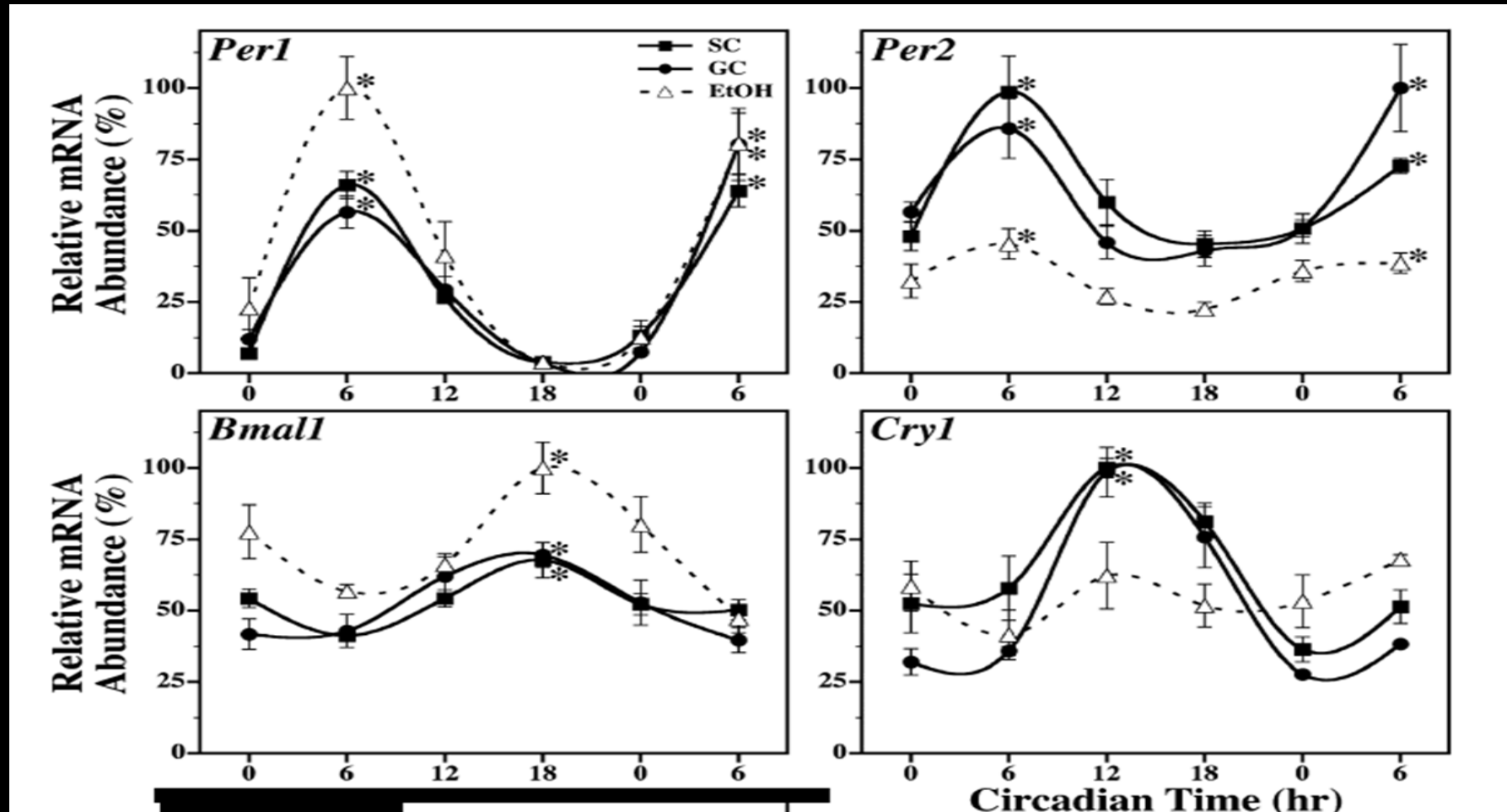
- Other “lesser” clocks occur in many organs (liver, adrenal gland, skeletal muscle, lung), regulate sleep, temperature, endocrine secretion, reproductive, immune. The “local clocks” have natural circadian cycles 21- 26 hours, They are synchronized by the SCN, but the pathways and mechanisms of this coordination aren’t fully understood. Without SCN peripheral clocks eventually dampen.

Clock Genes

- Alcohol during the prenatal period produces long-term changes in:
 - Circadian output signals from the SCN
 - Circadian rhythms of core body temperature and plasma corticosterone levels
 - BDNF

Clock Genes

Alcohol exposure during rapid brain growth

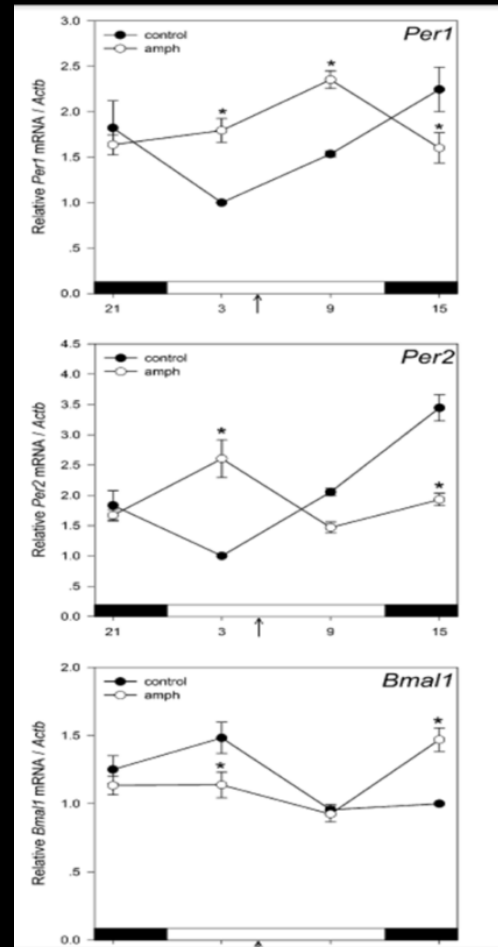


Clock Genes



- Prenatal alcohol exposure produces long-term changes in neural regulation of behavior including:
- learning difficulties
- attention deficits
- sleep-wake disturbances
- bipolar disorder and depression

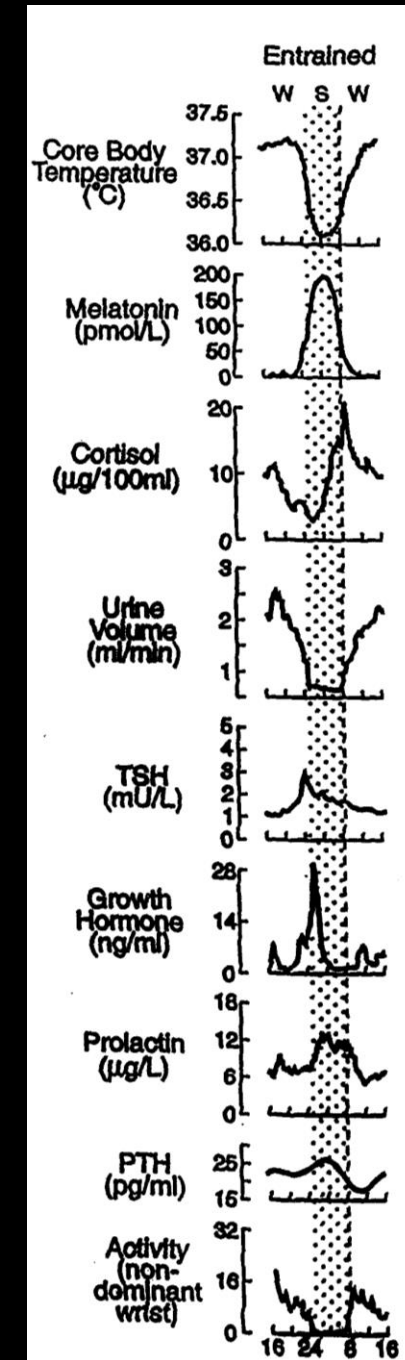
Clock Genes



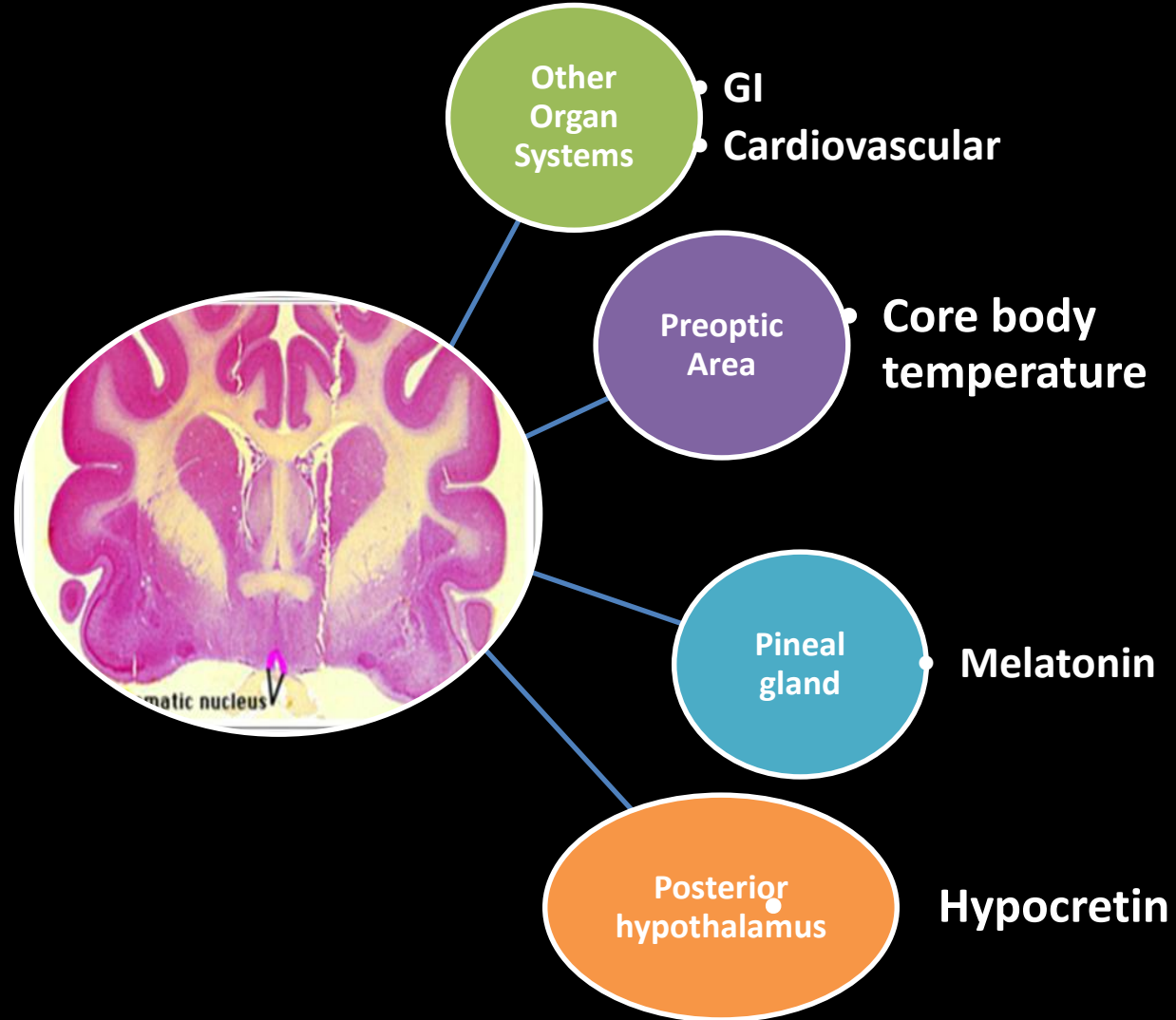
- Amphetamine induced change in Per1 and 2 reversed the expression from a nocturnal pattern to a diurnal pattern
- Bmal1 reversed from a diurnal to nocturnal pattern.

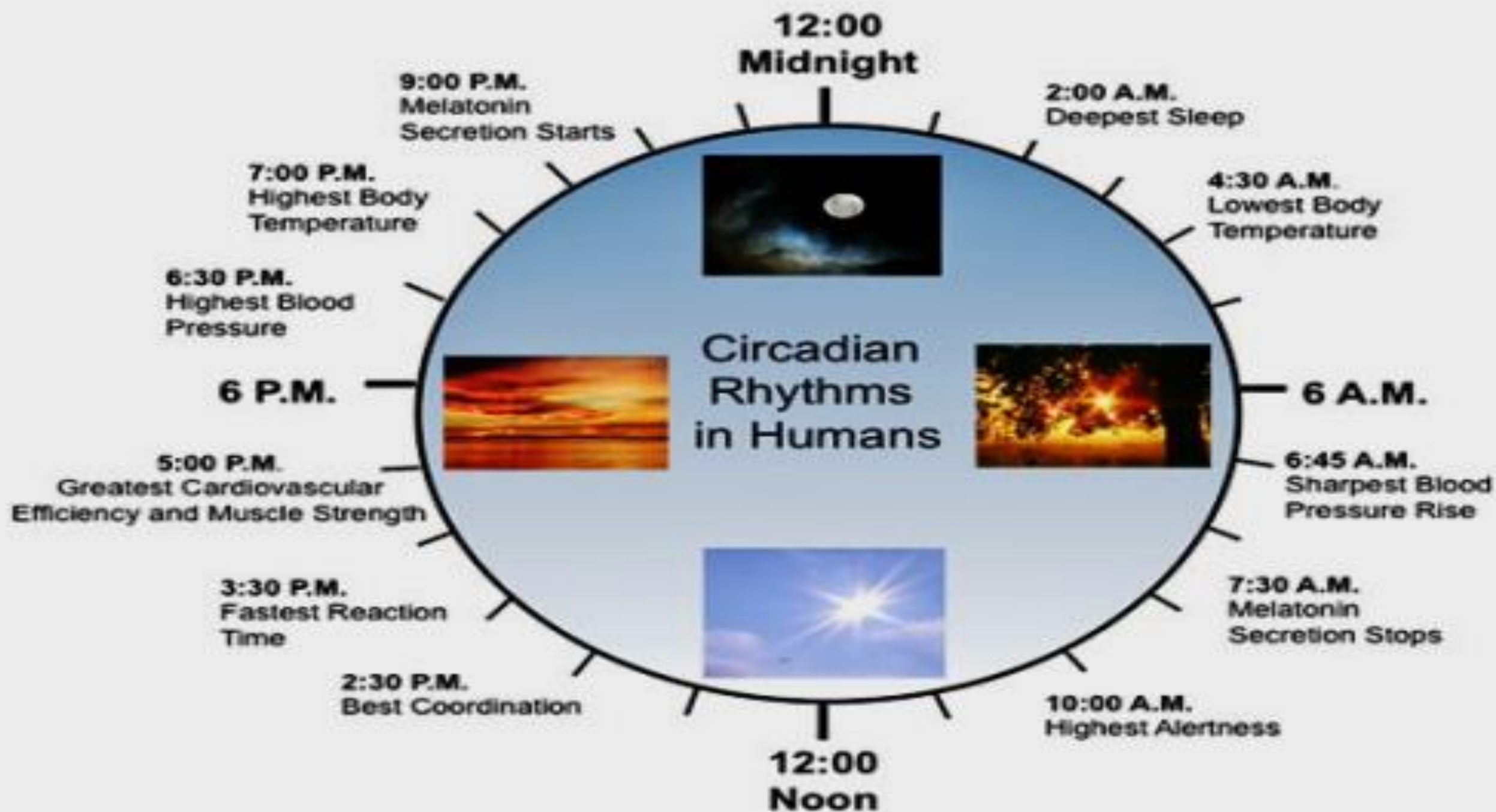
Circadian Entrainment (Synchrony) Best for Us

- Sleep/wake cycle;
- Subjective alertness, cognition and performance;
- Melatonin secretion;
- Core body temperature;
- REM sleep propensity;
- Gene expression;
- Brain metabolism;
- Plasma cortisol, growth hormone, prolactin, mTSH testosterone, and prolactin levels.
- Urinary volume, urinary potassium excretion, heart rate and blood pressure.



SCN Outputs





Our Clock Needs to Be Reset Daily

- SCN uses zeitgebers (time-givers or time cues) to help synchronize (entrain) or reset the clock daily;
- Key zeitgebers:
 - Light
 - Feeding Schedules
 - Activity
 - Melatonin



Circadian rhythms are under the control of the SCN re-sets our 24.2 hour day to 24 hours

Chronopharmacology: Timing of Medication Influences Toxicity and Efficacy

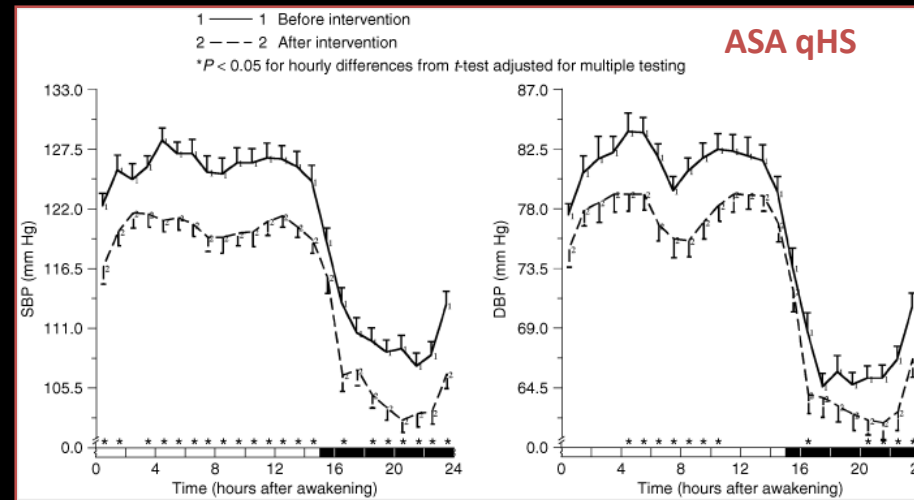
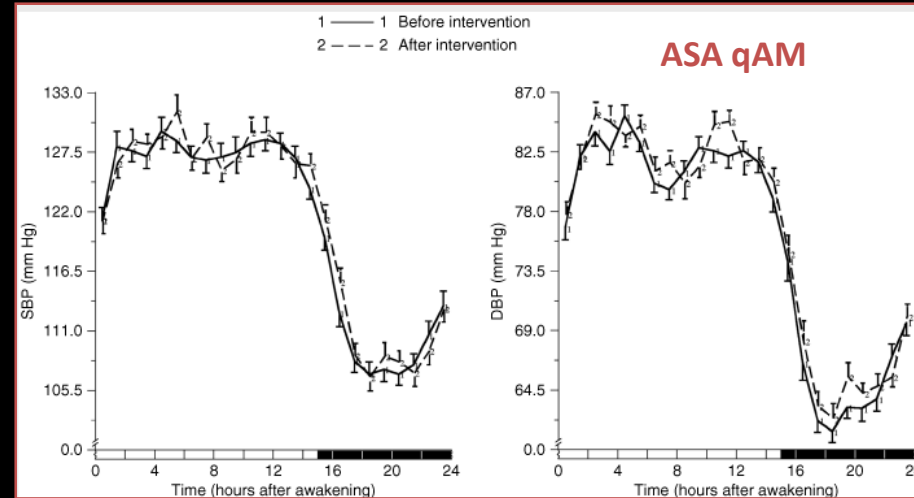
Morning	Evening or Before Bed
Methylprednisolone	Theophylline SR
Proton pump antagonist	Verapamil HCL
Testosterone drug-delivery patch	HMG-CoA-reductase antagonists
	H2-receptor antagonist
	Coumadin

- Programmed-in-time administration of tocolytics relative to the circadian rhythm in uterine contractility to avert preterm labor;
- Cancer chemotherapy to moderate toxicity and enhance dose intensity: 10% of a group of patients with ovarian cancer who received right drugs at wrong clock times were alive at 5 years vs. 50% who took them at the “right” times.

Prospective Study: Low-dose Aspirin Lowers Blood Pressure But Only When Taken at Night

- Mean decrease in 24-h mean SBP and DBP of 6 and 3 mm Hg without changes in heart rate in 244 patients with pre-hypertension who took ASA 100 mg PO qHS; not seen with dietary change or ASA qAM ($p < .001$);

- Low-dose valuable adjunct in lowering BP in patients with pre-hypertension or early hypertension but to be effective needs to be dosed at bedtime, ineffective when taken in morning.



Make take months or years to reset

- alcoholism
- depression

Know What You are Treating

Short Sleepers < 6 (5) hours

- It's not insomnia if it does not Impact Function
- Sergio Marchionne
- Chairman of Fiat sleeps 5 hours/night
- No loss of function

Long Sleepers > 9 (10) hours

Sleep State Misperception

- Often related to brain injury
- May be subtle i.e. small infarcts with age
- “I haven’t slept in 2 years”
- Fixed false delusion
- Cannot be changed
- Don’t treat
- Negotiate
- “Go to bed at 10 look at ceiling and get up at 6 or 8”

Fatal Familial Insomnia

- Less than 40 families worldwide
- Chromosome 20 –p13
- 179AA replaced by ASP
- 129methionine FFI
- 129 valine CJD

Insomnia of Childhood

- Who said “raising children would be easy”
- Limit setting disorder
 - Parents fail to set limits
 - Curtain Calling
- Sleep association disorder
 - Drive by babies
- Set bed times
- No TV in the bedroom
- Early wake times

Sleep Deprivation and Self induced Insomnia

- Society addicted to staying awake
- Chronic sleep deprivation
- Poor sleep habits
- Blue light
- All self – induced
- Individuals must make a commitment to sleep

Re-training Proteins

Self Induced Insomnia

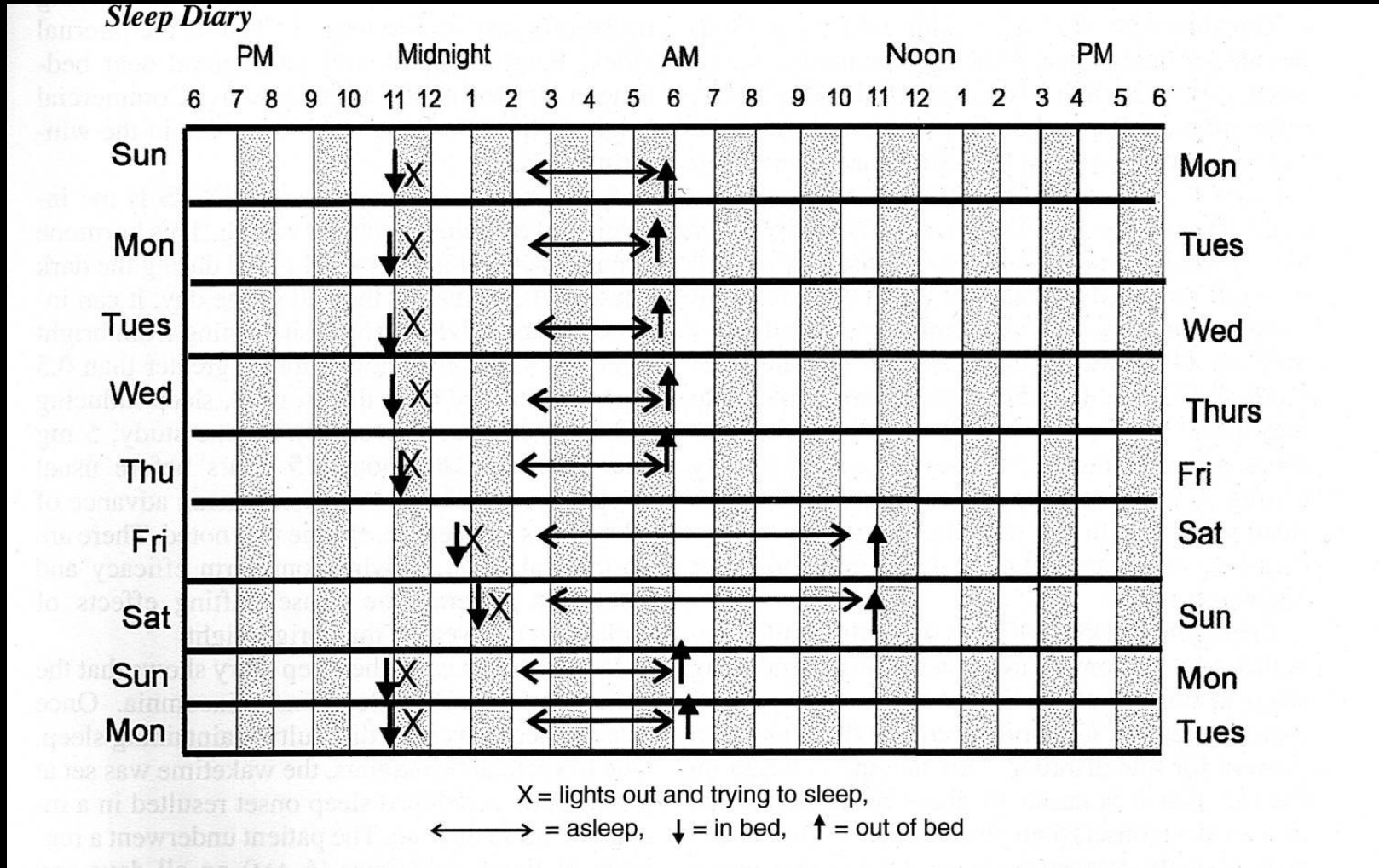
The Role of Blue Light and The Need to Stay Awake



- Nighttime work
- Nighttime television
- Computers
- Cell phones
- I Pads

Self Induced Insomnia

Sleep Logs – note the extra 3 hours of sleep on weekends



Sleep Restriction (not enough sleep)

Common Symptoms

- Excessive daytime sleepiness
- Wake up feeling unrested
- Excessive loud snoring
- Problems with memory and concentration
- Depression
- Difficulty controlling pain
- Frequent headaches

Children

- Is your child hard to awaken in the mornings?
- Is your child falling asleep in school
- Difficulty paying attention in school
- Hyperactivity
- Aggressiveness

Sleep Restriction (not enough sleep)

Ask

- How many hours do you sleep?
- What time do you go to sleep?
- What do you do the hour before you go to sleep?

It's Not Insomnia

- Hard to awaken in the morning?
- Falling asleep during school or work?
- Go to bed earlier!

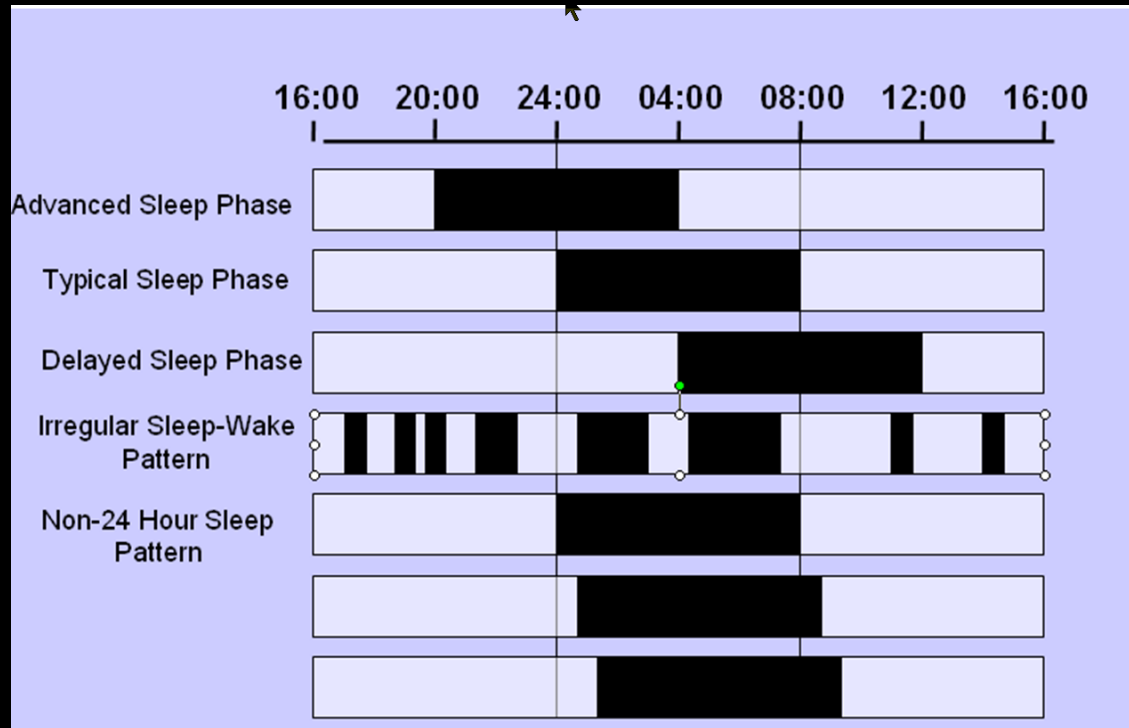
Insomnia

- A disorder of hyperarousal
- A disorder of training CLOCK proteins to act abnormally
- Society addicted to staying awake

Insomnia and Circadian Rhythms

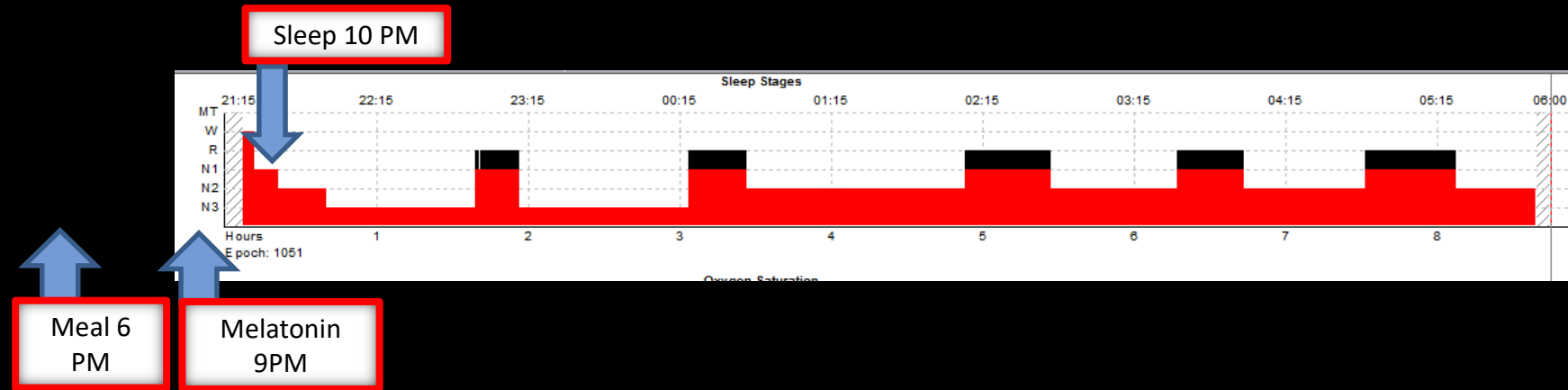
- Percentage of people with hyperarousal disorder is minimal
- Created to sleep sufficient hours
- Created to wake sufficient hours

Common Circadian Rhythm Disorders



Essential problem: misalignment internal sleep/wake rhythm and the desired (or required) time for sleep → desire for sleep and wakefulness at inappropriate times, some types of insomnia, and excessive sleepiness.

NORMAL SLEEP PATTERN

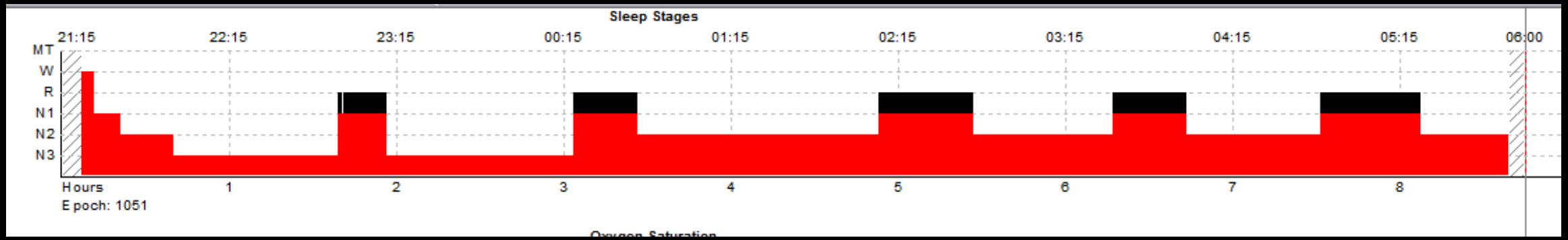


When it is not Insomnia

- Advanced Sleep Stage Early Sleepers
 - Elderly
 - AD
 - NH
 - Normal

Typical Sleep Time

- Typical sleep time



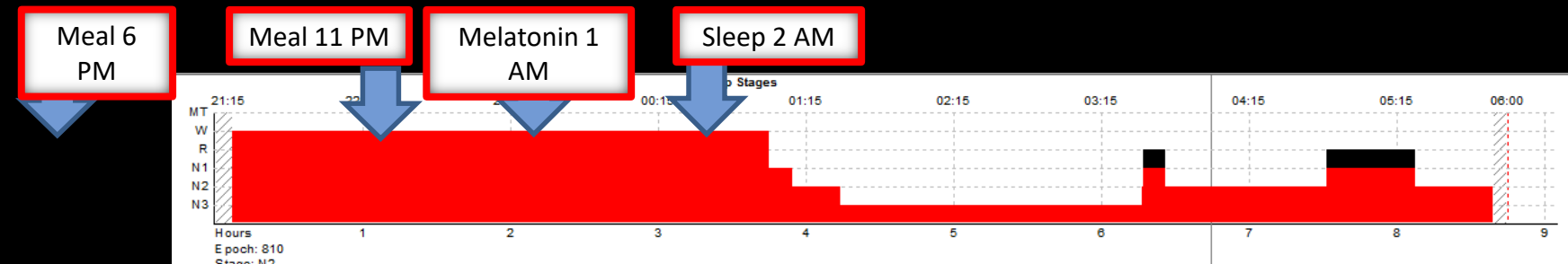
Insomnia and Circadian Rhythms

- Delayed sleep phase
 - High school
 - Young
 - Driven doctors w/o healthy boundaries
 - Normal

NORMAL SLEEP PATTERN



DELAYED SLEEP PATTERN



Insomnia and Circadian Rhythms

Irregular sleep wake pattern

- Key: count the hours of sleep in 24 hours.
- Poor sleeping habits
- Dementia
- Do not give sleeping agents

Insomnia and Circadian Rhythms

- Free Running Clock
 - Blind individuals

Insomnia and Circadian Rhythms

Don't treat

- Poor sleep habits
- Not enough sleep time

Treat

- Sleep plenty of hours and the patient is still sleepy
- Exclude sleep disorders such as:
 - Sleep apnea
 - Narcolepsy
 - Thyroid disease
 - Anemia

Medications for Sleep

FDA Approved

- Ramelteon
- Doxipin
 - Brand name (Selanor) 3-6 mg vs generic
- 5 Benzodiazepines
 - temazepam
- 3 NBNZOS
 - Zaleplone T $\frac{1}{2}$ 1
 - Zolpidem T $\frac{1}{2}$ 3
 - Ezoplicon T $\frac{1}{2}$ 6
- Suvorexant

Off Label

- Trazadone 25-100 mg
 - Bi-modal metabolism
- Anti-histamines
- Seroquel
- Mirtazipine

Conclusion



- SCN is the “master clock”
- Clock genes regulate the clock
- Circadian rhythms regulate amount of sleep needed
- Most common type of insomnia
Self induced
 - Turn off the blue light
- Shift sleep times with light and melatonin