Circadian Update

This is the Rhythm of the Night

Caris Talburt Fitzgerald, MD

Accreditation Statement

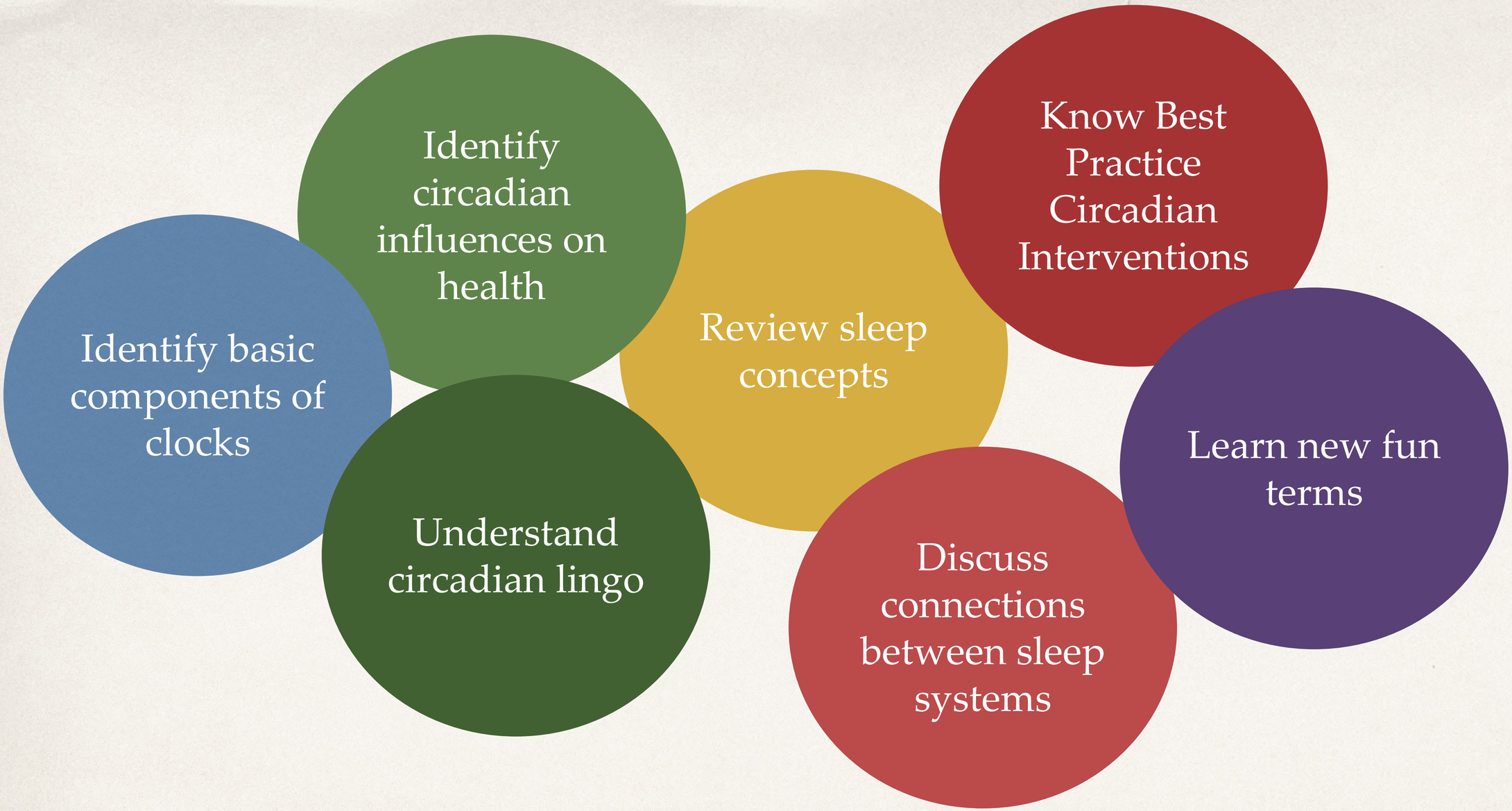
This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of The American Academy of Sleep Medicine and the Sleep Professionals of Arkansas & Washington Regional Center for Sleep Disorders. The American Academy of Sleep Medicine is accredited by the ACCME to provide continuing medical education for physicians.

Conflict of Interest Disclosures for Speakers

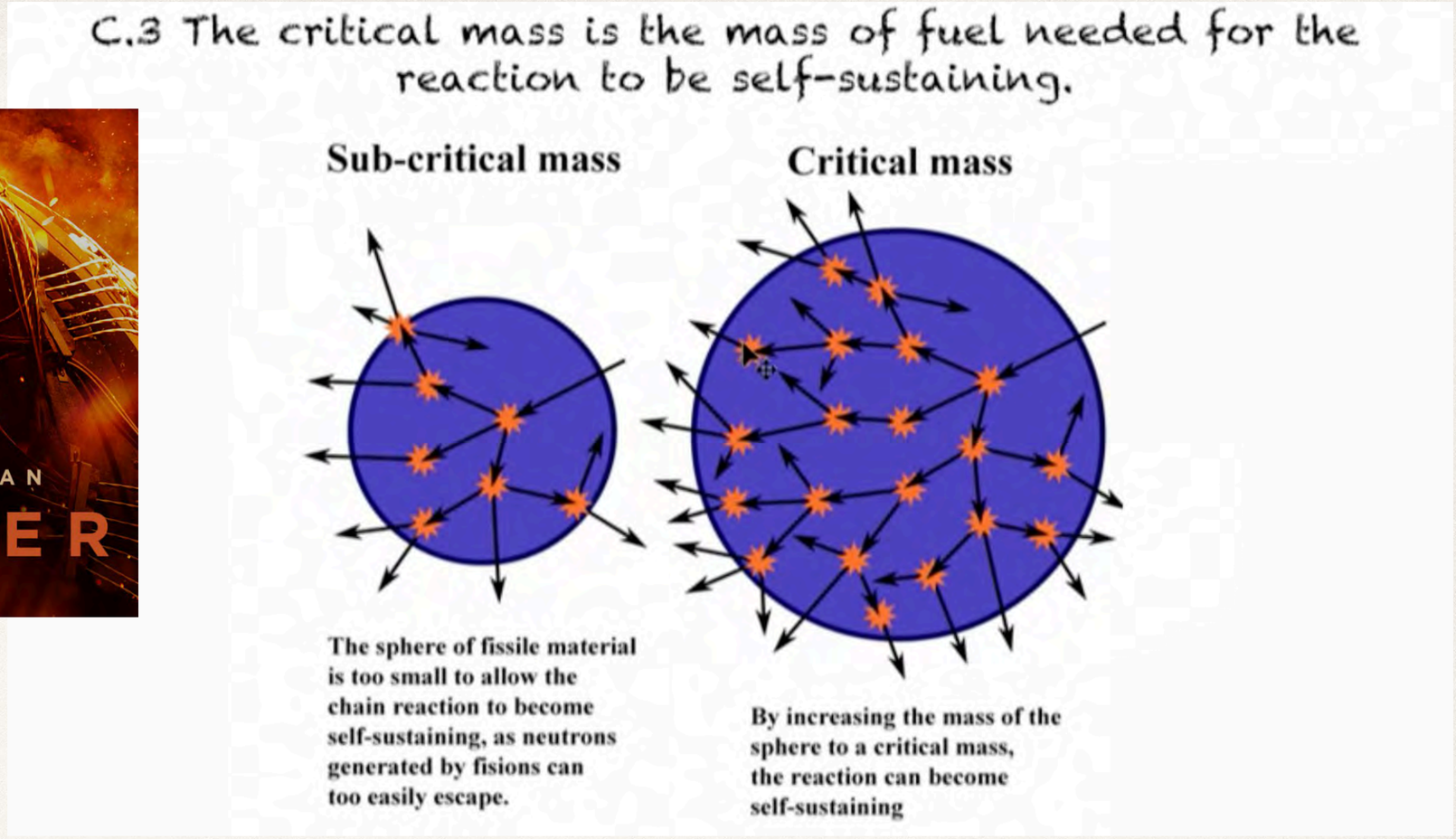
Caris Talburt Fitzgerald, MD has no relevant financial relationships with ineligible companies to disclose.

Learning Objectives

- Discuss known components of the Circadian system
- How it impacts various parts of the body
- Understand various inputs to the clock



Map for Today



Criticality (Mass Need for Optimized Function)

A state that optimizes thinking and processing **(homeostatic end goal** for networks in the brain) wake pushes the brain away from Criticality

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In Nuclear Fusion this is the condition in a nuclear reactor when the fissionable material has enough mass that it can sustain a chain reaction by itself

Criticality (Sleep restores the computational power of the Brain)

A state that optimizes thinking and processing (**homeostatic end goal** for networks in the brain) wake pushes the brain away from Criticality

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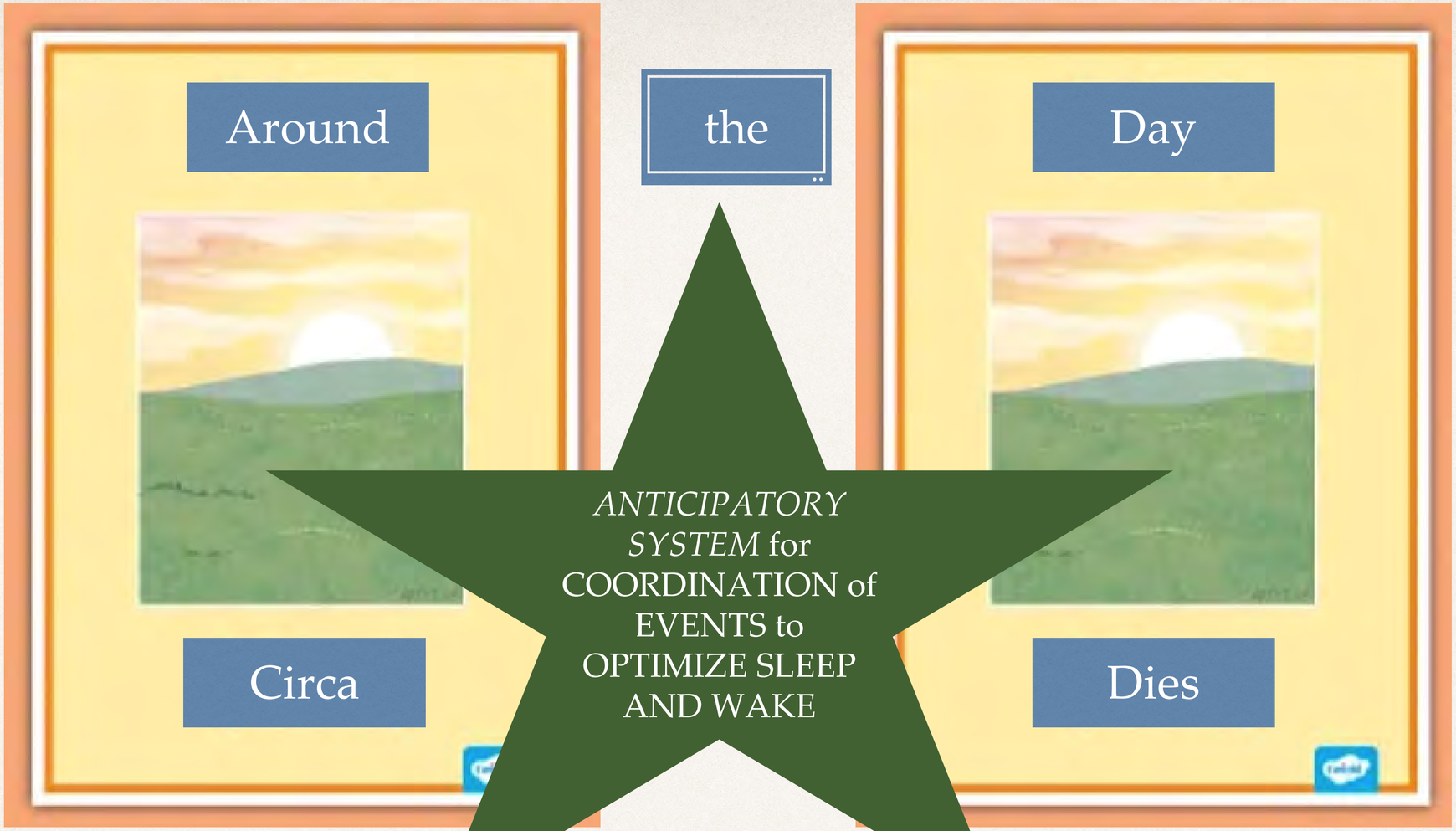
Circadian Rhythm allows for preparation and anticipation of when peak performance (optimized) will be needed and when it is safest to turn energy inward



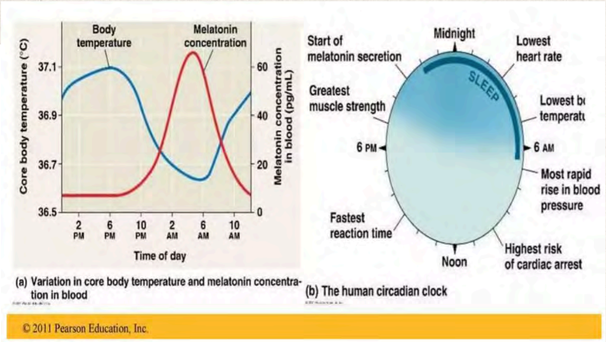
Latin Origin meaning Around the Day

All rhythms are named based on our relationship to light

1 CIRCADIAN RHYTHMS

cycles occur every 24-hours

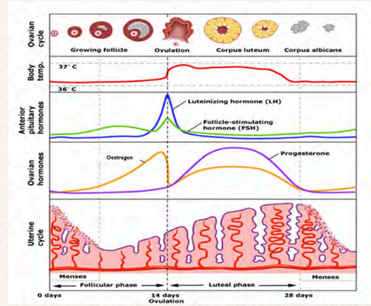
24HRS



2 INFRADIAN RHYTHMS

cycles are longer than a 24-hour period

LESS FREQUENT

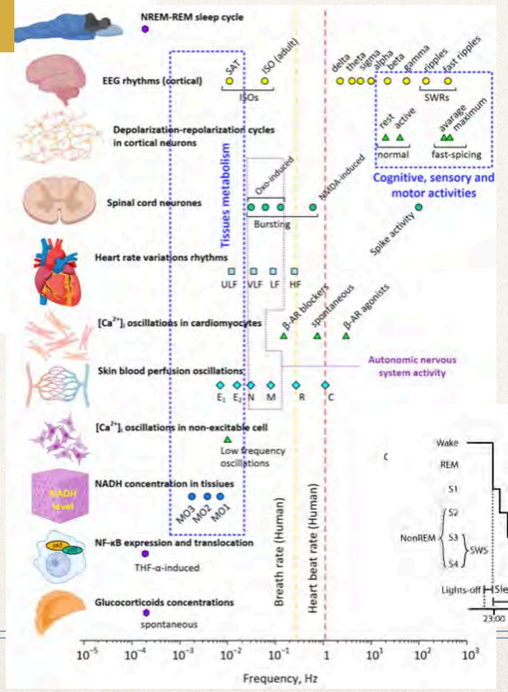


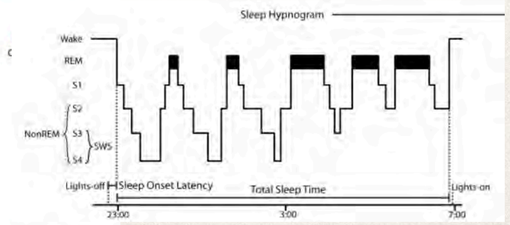
AKA
Circalunar (q30days)

3 ULTRADIAN RHYTHMS

have multiple cycles within a 24-hour period

MORE FREQUENT

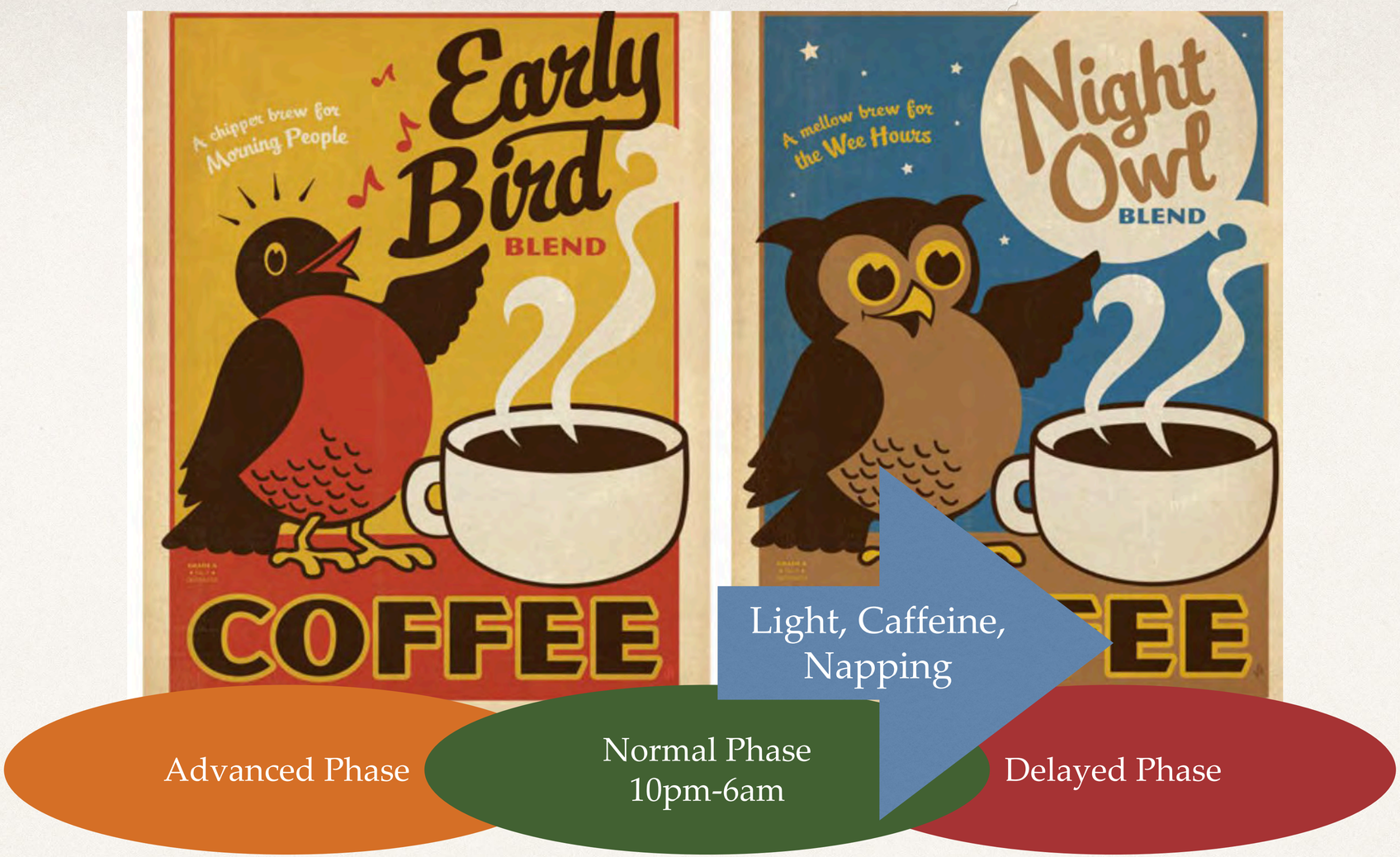




Rhythms of Life

Circannual means once/year (Migration or Hibernation)

REM Sleep Periods are Ultradian and considered to be under Circadian Control



Chronotype

"Advanced Sleep" is the Early Bird or Morning Lark , "Delayed Sleep" is the Night Own

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The Cure for Phase Delay is called "Phase Advancement" into a Normal Phase of Sleep and requires very specific strategies

BEST SLEEP

KEY TO SUCCESS
Address all of these issues over a two week period or longer if having to change the phase of sleep

SLEEP DRIVES

Homeostatic
Timing
Napping
Exercise
Caffeine

Controls NREM 3

Circadian
Timing
Light
Needs 2wks

Controls REM

AROUSAL

OSA/UARS
GERD/LPR
Sensory Input
Emotions
Meds
Substances
Excess time in Bed

OSA is the Elephant in the room, if not treated behavioral interventions will fail

Avoid bright light the hour before bed and during the night

KNOW
NREM3 controlled by Homeostat
REM controlled by Circadian Phase

Mechanisms of Sleep

Best Sleep is Created when Arousal is Very Low and Sleep Drives are Very High

Need 2wks of consistency with the Circadian Rhythm to help this sleep/wake system grow strong

Paris was the first city to be electrically lit in 1841

Electricity and Our World

We now exist in a world with dim days inside and brighter lights at night

1880 Edison began selling the light bulb and by 1892 he had over 3 million customers, 1930s New Deal brought us electrical power grids.

Bright Light at Night
Delays Rhythm
Work/School Limits Sleep
Delay Reinforced on Weekends

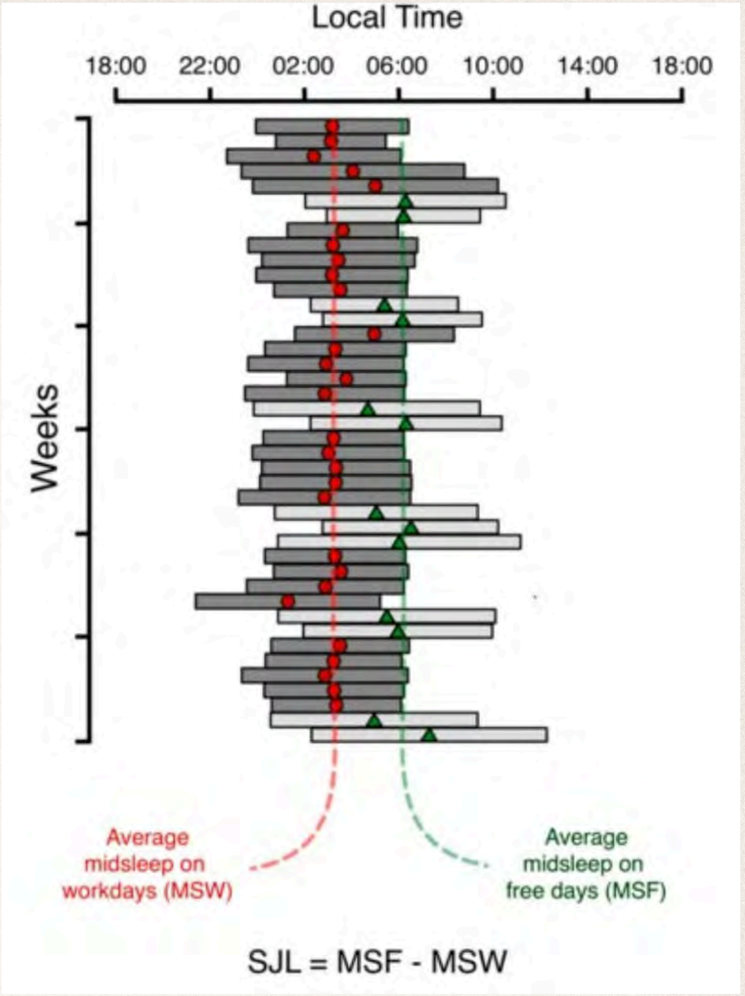
LEADS TO
Self Imposed Sleep Restriction
Use of Caffeine
Napping
Sleeping in
Lower Physical Activity Levels
Worse Diet

Social Jet Lag

Often ends up impairing both sleep drives

"I have problems getting to sleep" or "I am too sleepy/fatigued in the day" or "I can't concentrate" ***-fix the Jet Lag First***

Adolescences with greater misalignment are more likely to use illicit substances and be involved in an MVA

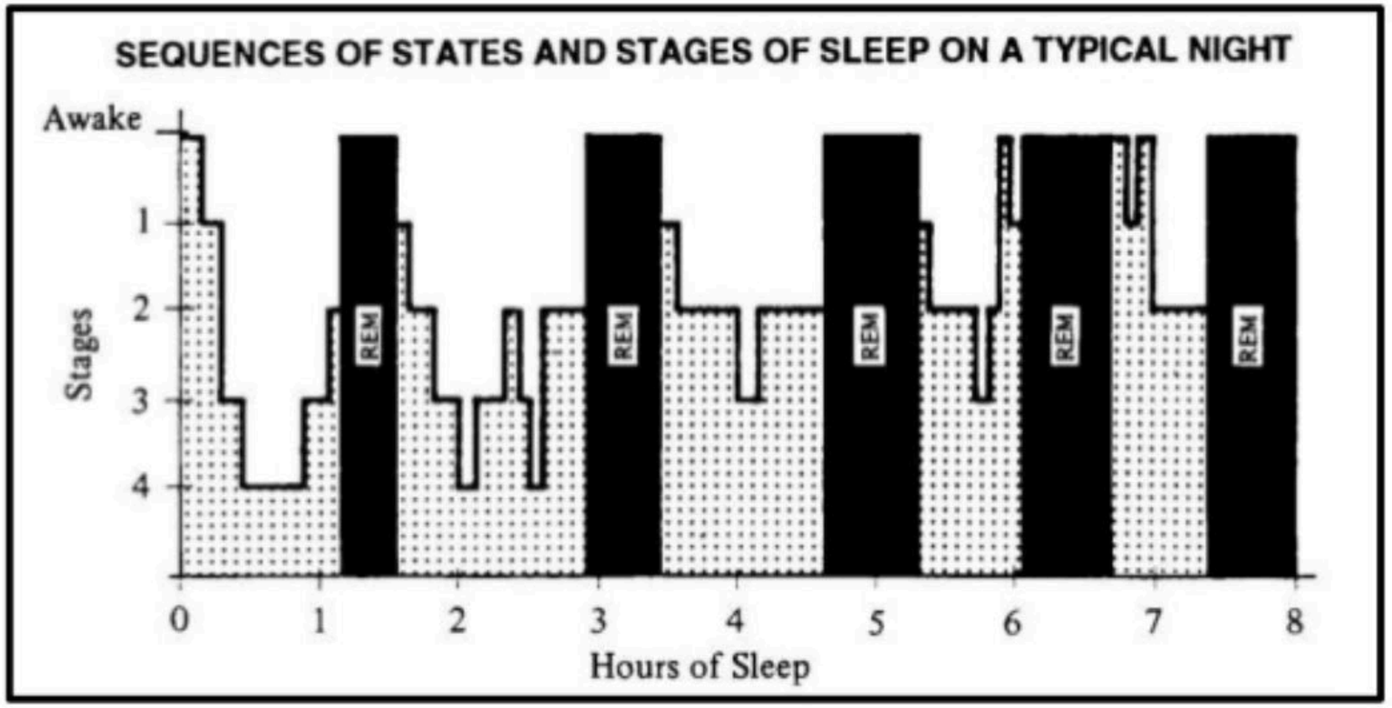


Social Jet Lag and Substance Use

Different sleep times during the work week than the weekends associated with increased tobacco, caffeine, and alcohol consumption

German Research Till Roennenberg 2006

Normal Sleep Hypnogram



This causes false negatives for OSA and false positives for Narcolepsy

SOREMPs on MSLTs are more predicted by usual timing of sleep than any other marker

REM follows Circadian Timing

That means the night owl has a good chance to get misdiagnosed

Atonia of REM means, REM is where OSA is usually present

This is why sleep studies have to have 20-25% REM to be "Adequate"

It will take time to "Lock In"

Two Weeks

Don't tell them to just wake up earlier

Advanced Phase

Normal Phase
10pm-6am

Delayed Phase

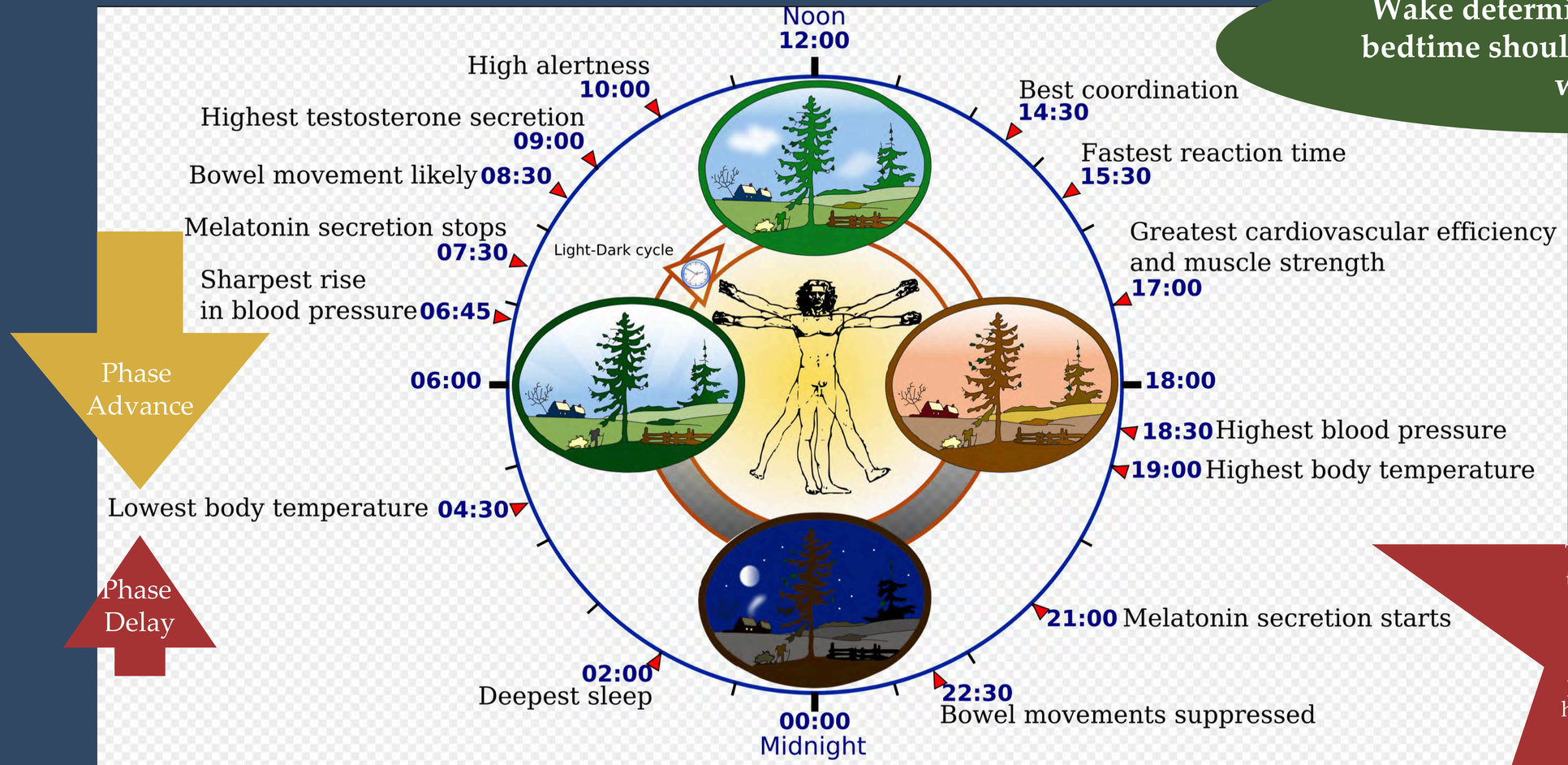
Phase Advancement the Treatment

Move Wake in 15min Increments, Light and Exercise Upon Waking (Stop when waking before the Alarm)

Careful attention to Light at Night, Avoidance of Caffeine, Napping, and Sleeping In, 3mg 4pm Melatonin

Chronobiotic

Wake determines bedtime, but bedtime should NOT determine wake



THE BTN follows timing of sleep so you can further phase delay someone who is phase delayed by having them wake too early

Circadian Clock

Bright light on the morning side of Body Temp Nadir (BTN) Advances Sleep while on the other side it Delays Sleep

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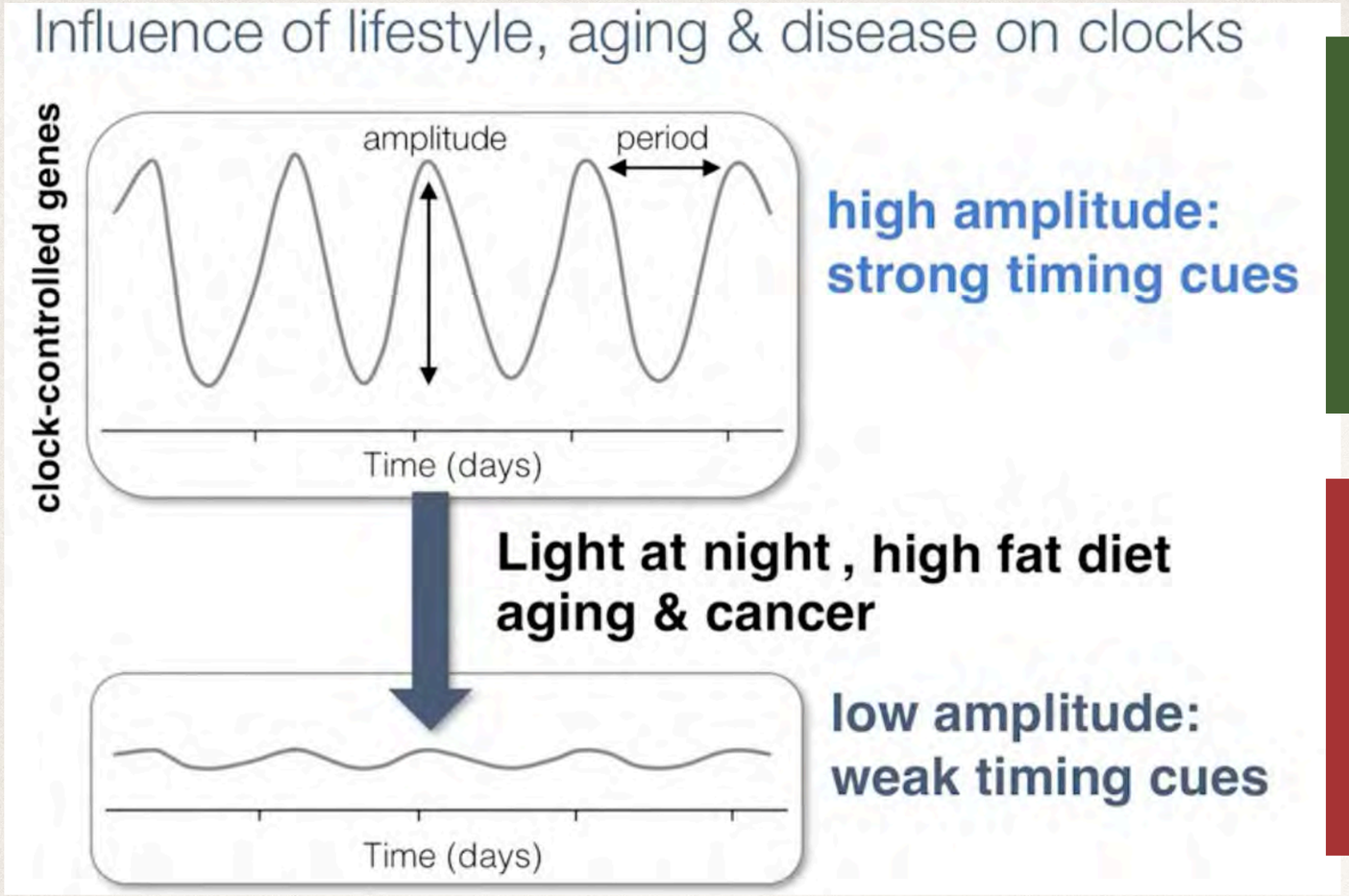
*The closer the bright light to the BTN **the stronger the influence**, which is why morning light is so very important to reset our clocks each day*



SAFETY
SYSTEM OPTIMIZATION

THRIVE

DANGER
FLEXIBILITY

SURVIVE

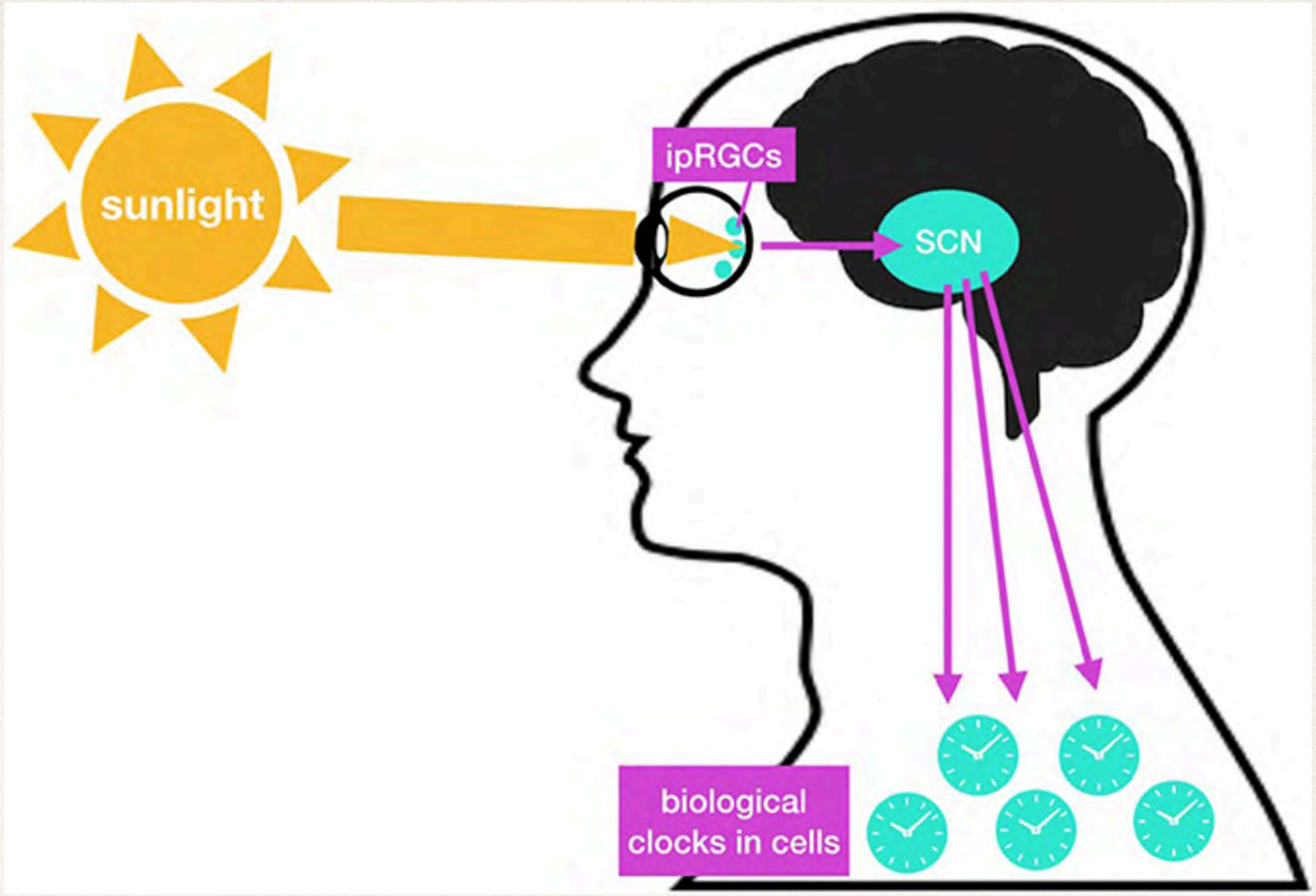
Circadian Amplitude

Amplitude is power/push into both sleep and wake with the Circadian System

Low Amplitude allows for us to do what we need/want to do when we need/want to do it and High Amplitude allows for us in a safe and secure environment to thrive

ZEITGEBERS
Pronounced
Zite ghee burrs

Light
Food Intake
Posture
Activity



Retino Hypothalamic Tract

External (Sun weakened by DST), Internal (Biologic weakened artificial light and indoor habitation), Social (moved us toward delay

SCN forwards the rhythmic signal via the Hypothalamus-Pituitary-Adrenal (HPA) axis and the autonomic nervous system

This is also why sedatives work best when taken at an optimum time

Maximum Potential Energy

Equilibrium

Alignment of Sleep Drives

Properly Timed Melatonin similar to pushing a swing at its location of Maximum Potential Energy

Delayed Melatonin similar to pushing a swing while standing below it at its point of Equilibrium

Children are highly sensitive to melatonin suppression in response to evening light (Hartstein 2022)

Indoor Sunset Transitions

During Daylight Savings it needs to be an hour darker inside than out

OTC Melatonin is only hitting one of 10 or more neurotransmitters. *Sedation is not the same as sleep.* *Habits have to be right for success.*

75% Favor Ending a Switch
DST makes it harder to go to sleep
Exacerbates Phase Delay
Worsens Social Jet Lag

Showing the Power of Light and Sleep

DST Results in
Less Sleep
Increased MI, CVA, Afib
MVAs (Increase 22%)
More Suicides

Daylight Savings

Lose an hour (24%Increase in MI) Gain an hour (21%Decrease in MI) -data from over 300million people

DST in 1974 Reversed in months secondary to how long it stayed dark in the mornings in the winter and the dramatic increase in school bus stop fatalities

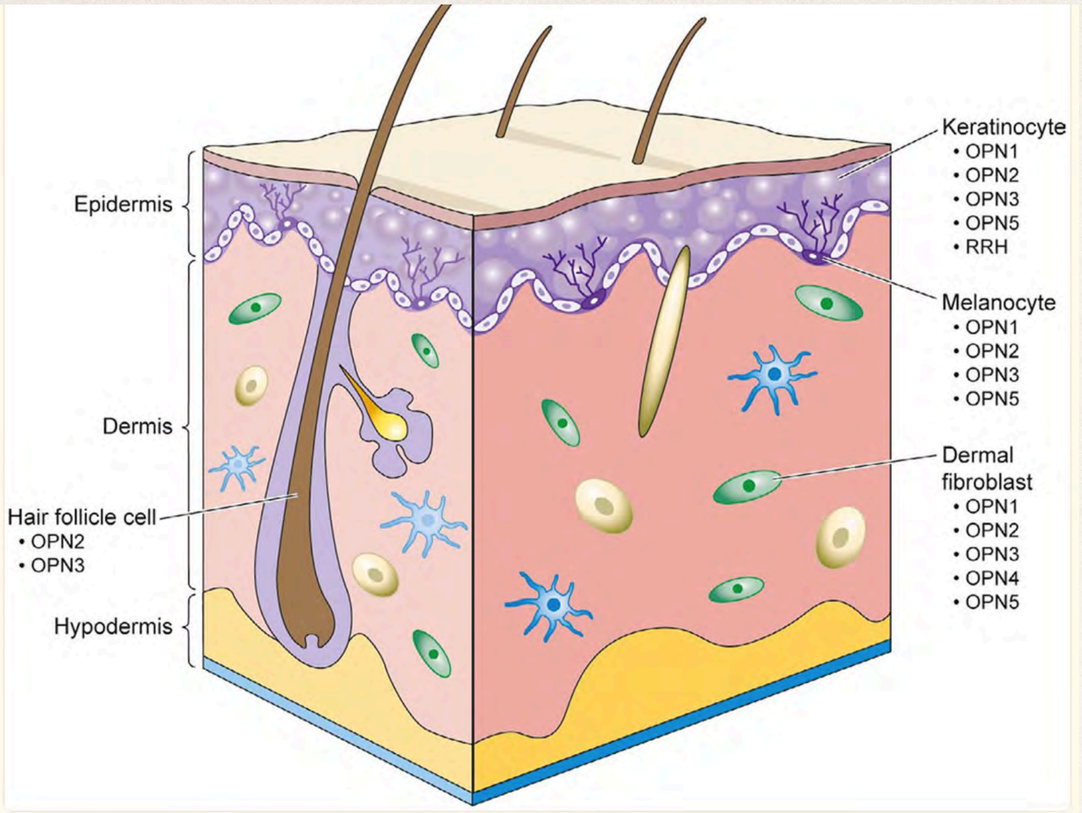


FIGURE 2

The expression of opsins in human skin cell types [Colour figure can be viewed at wileyonlinelibrary.com]

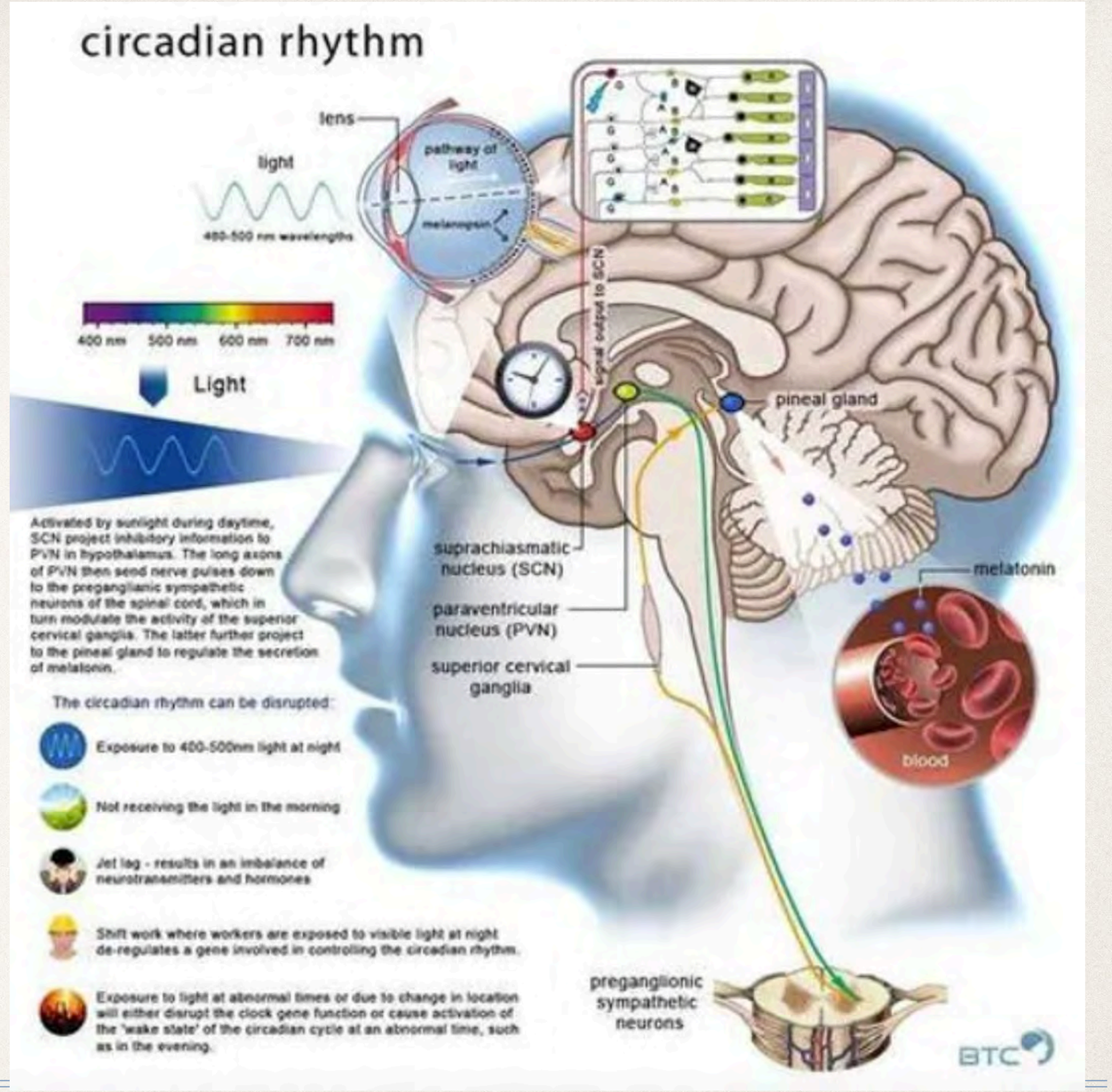
Photobiomodulation (PBM)

Form of Nonionizing Light Therapy used for a variety of Dermatologic reasons (Psoriasis, Dermatitis, Hair Regrowth, Wound Healing, and Tissue Regeneration

AKA Low Level Laser Therapy (LLLT) can induce cell proliferation, enhance stem cell differentiation, and decrease inflammation

SCN

Receives from and Transmits to Variety of Sources

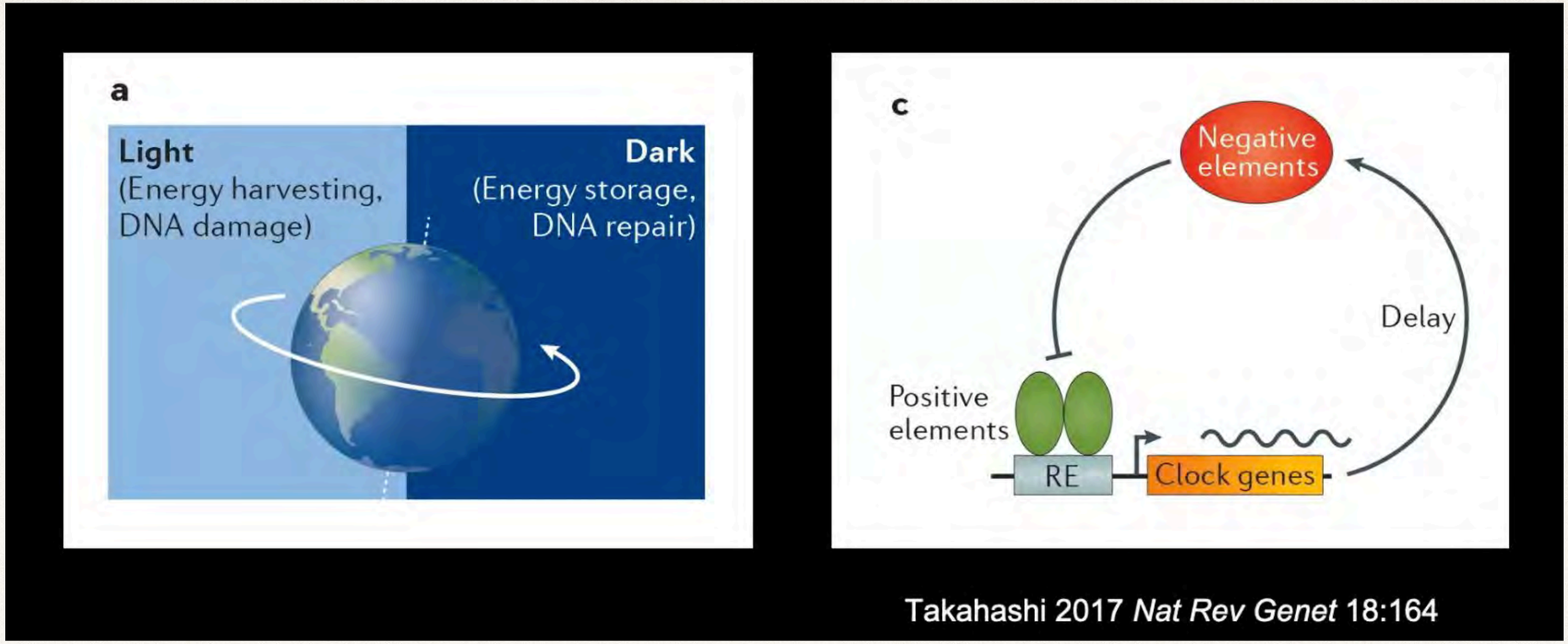


Light is not our only Zeitgeber and ***Melatonin is not the only circadian coordinator***

Orexin (aka Hypocretin) is a Wake Promoter

Telling Time by what you ate, light, and levels of arousal (flight for fight) located near SCN

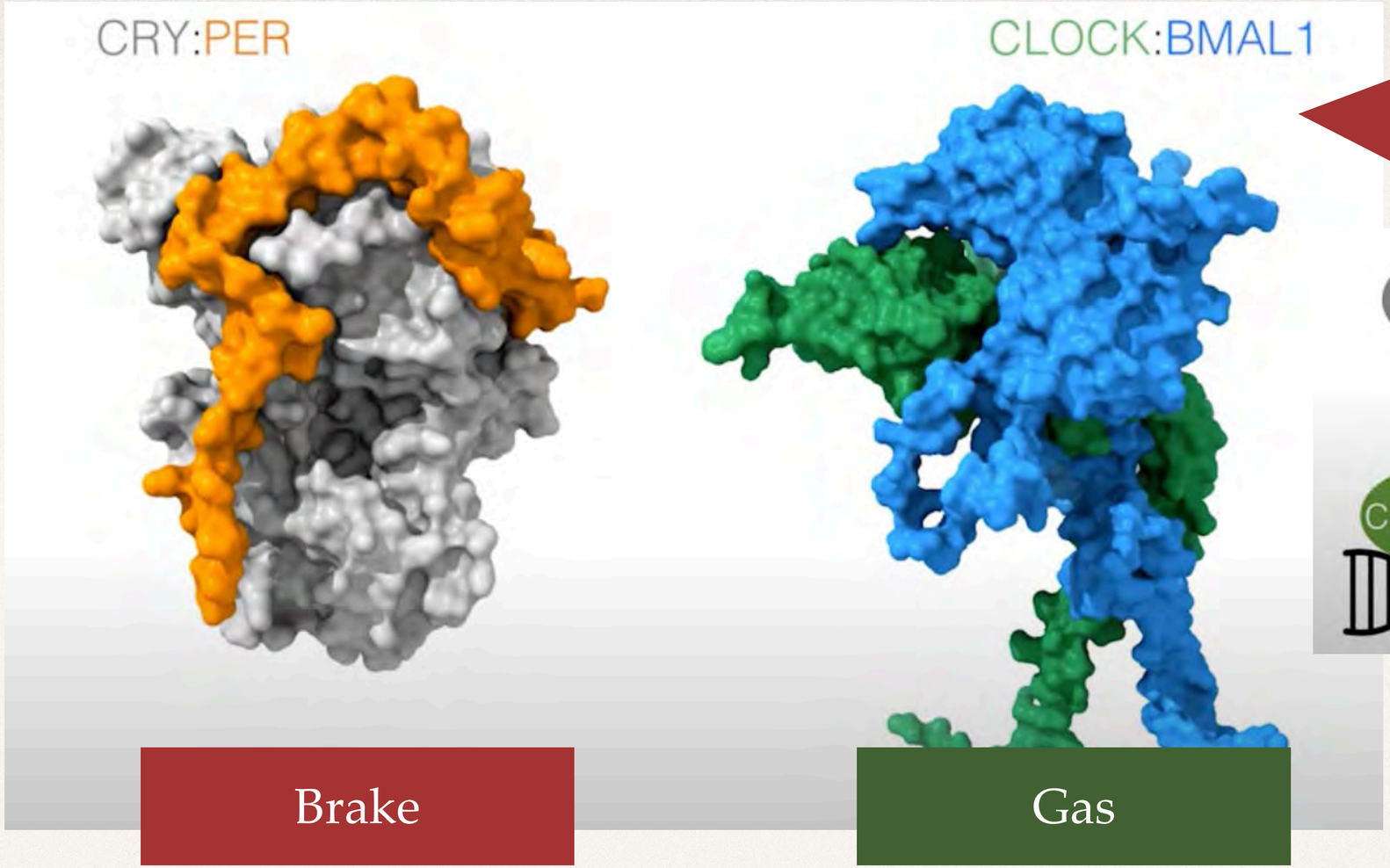
Wake Promoter, Increases Activity, Energy Expenditure, and Feeding (greatest activity in wake, silent in NREM, and burst activity in REM)



Influence of Light on a Molecular Level

Neurotransmitters are working cell to cell, but inside the cell there is a whole other circadian biochemical process going on

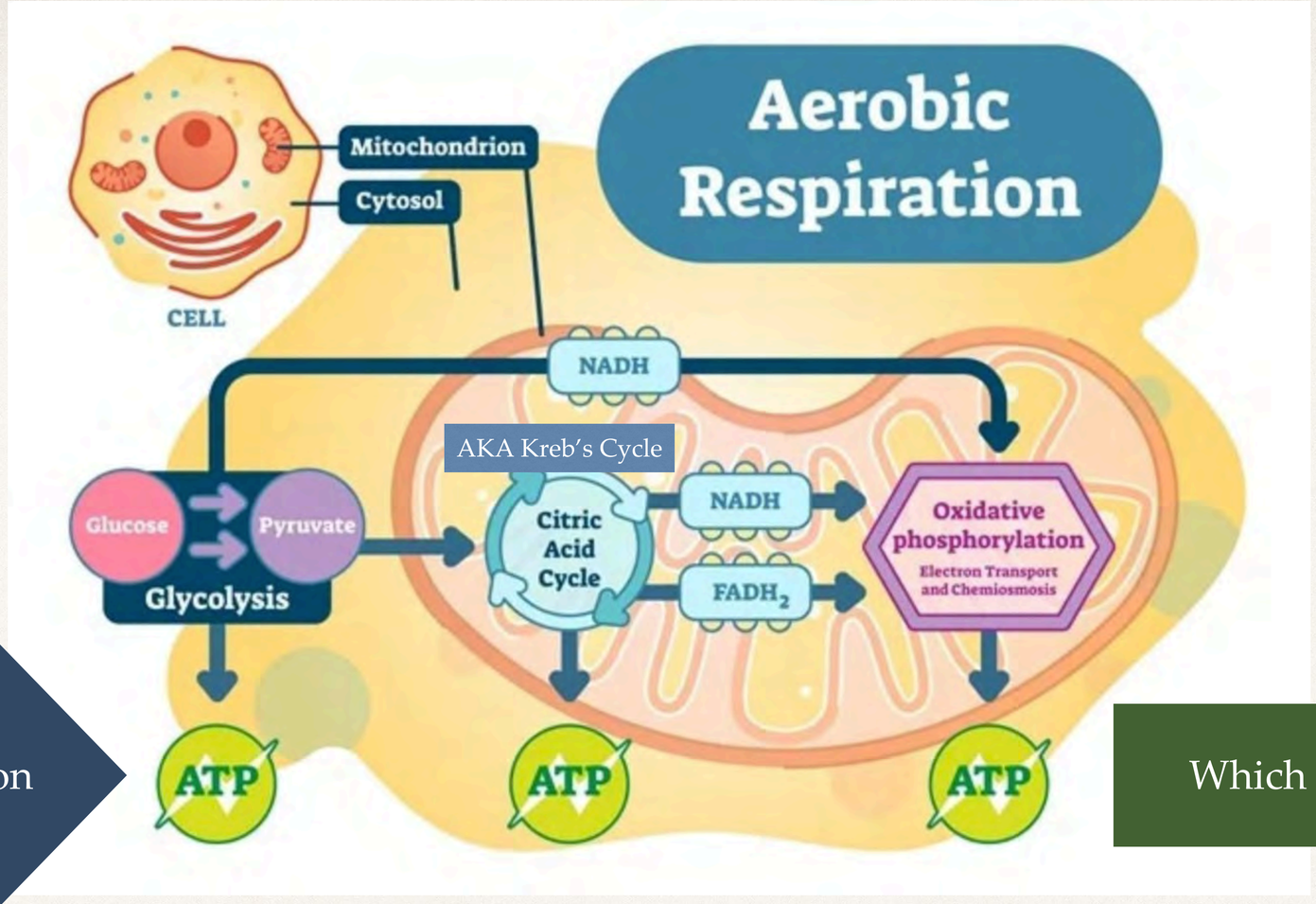
The Biochemistry of Body Clocks



Feedback Loop of Clock Proteins

Cryptochrome and Period as "the Brakes" of the System and Clock and Bmal1 as "the Gas"

Clock Makes Per and when enough Per accumulates it deactivates Clock (which helps us fall asleep) that causes Per to drop which allows expression of Clock to build back up Per



End Goal is Energy Production

Which Fuels Everything Else

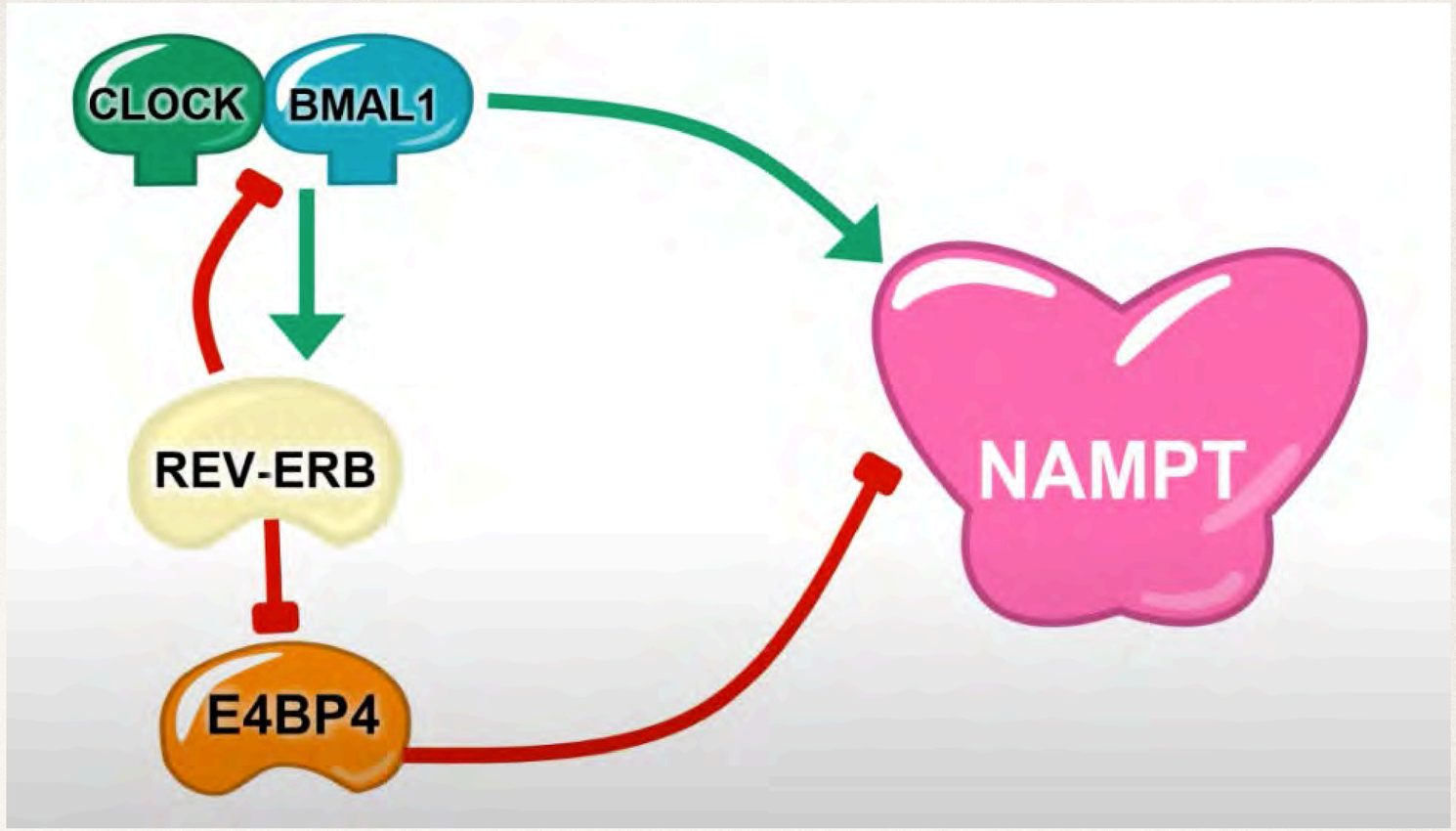
Aerobic Respiration

Requires Glucose, Enzymes, Cofactors, and Oxygen, and produces Energy, Carbon Dioxide, and Water

Adenosine Triphosphate (ATP) can have its phosphate bonds broken to fuel almost all other reactions

NAD+
Energy Molecule
Used to make ATP
Electron Carrier
Cofactor for Enzymes
Involved in Repair

Fatty Acid Oxidation
Glycolysis
Krebs Cycle



Vitamin B3

NAMPT (converts NAM to NAD+)

Clock Controlled Nicotinamide Phosphoribosyltransferase is the rate limiting enzyme for the production of NAD+

Critical for Cellular Metabolism, ***Circadian Disruption leads to decreased expression and arrhythmicity of NAMPT***

Biology (Basel). 2017 Mar; 6(1): 10.
Published online 2017 Feb 4. doi: 10.3390/biology6010010
PMCID: PMC5372003
PMID: 28165421

Circadian Rhythms and Hormonal Homeostasis: Pathophysiological Implications

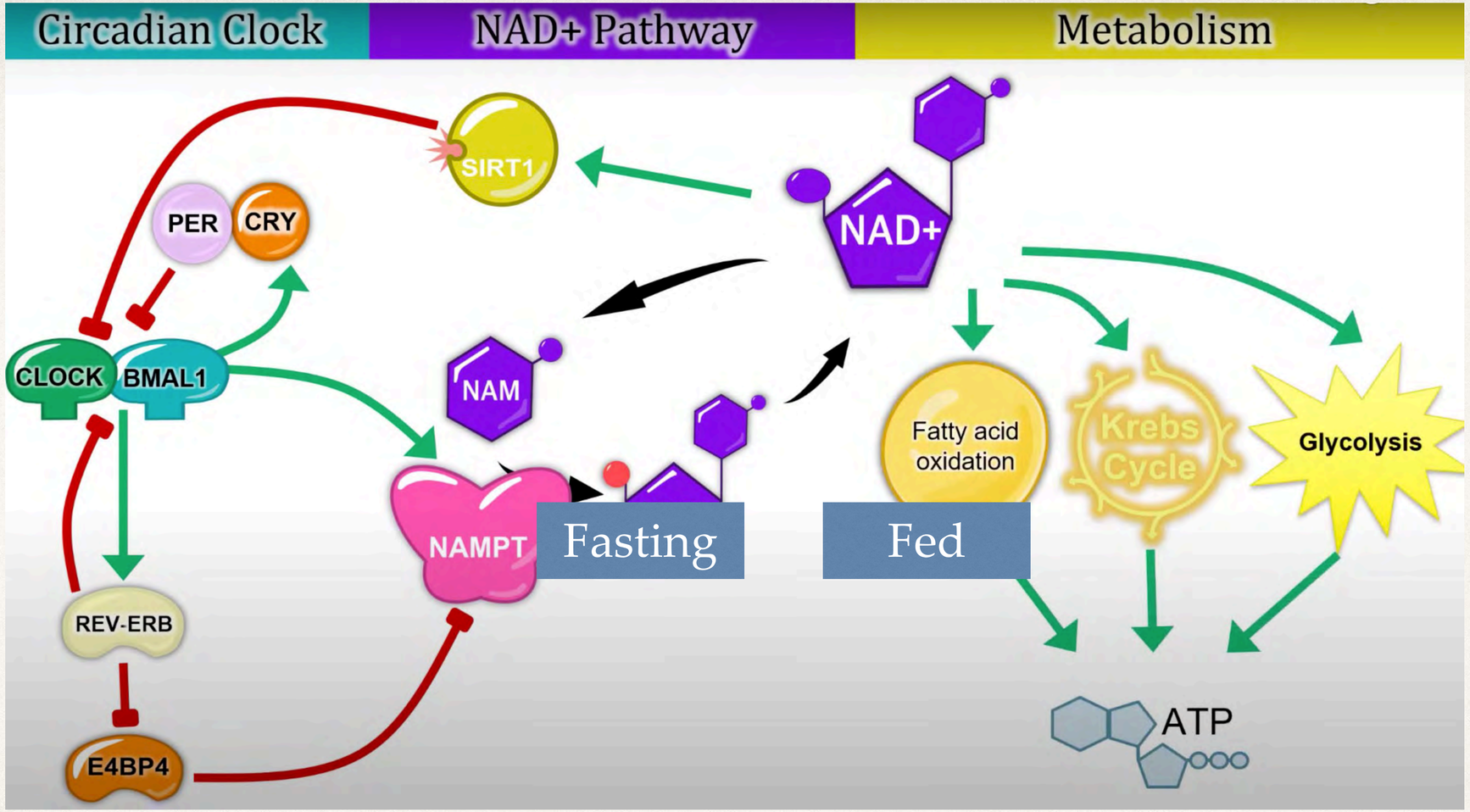
Davide Gnocchi[1,*] and Giovannella Bruscalupi[2]

Sirtuin1

Longevity Gene, Increased by Fasting, Modulates Rhythmic Expression of Circadian Genes

A central role was attributed to SIRT1, a member of SIRT deacetylase family, whose activation has been related with many positive effects [151]. SIRT1 activity requires the presence of NAD^+ as a cofactor, consequently, during fasting, when NAD^+ level is elevated, SIRT1 activity is high [151]. SIRT1 modulates the rhythmic expression of numerous circadian controlled genes. NAD^+-dependent histone deacetylation mediated by SIRT1 of BMAL1 and PER2 enabled the establishment of a repressive chromatin state [152]. SIRT1 binds with CLOCK and is recruited at the CLOCK·BMAL1 chromatin complex at circadian promoters. Genetic disruption of *Sirt1* or pharmacological inhibition of SIRT1 desynchronised the circadian cycle: so SIRT1 might play a role as a controller of the circadian machinery, perceiving modifications in cellular metabolite level [153]. Of note, intracellular NAD+ levels exhibited circadian oscillations, as a consequence of the circadian expression of nicotinamide phosphoribosyltransferase (NAMPT) mediated by CLOCK·BMAL1. SIRT1 is then recruited to the *Nampt* promoter, directing the synthesis of its own coenzyme [154]. SIRT1 is also involved in the regulation of circadian transcription of numerous clock genes, namely *Bmal1*, *Per2*, *Cry1*, and *Rorγ*. SIRT1 binds CLOCK·BMAL1 and promotes PER2 deacetylation and degradation. Because its deacetylase activity is dependent upon NAD^+ levels, SIRT1 may function as a connector between cellular metabolism and the circadian machinery [155]. Interestingly, it was shown that SIRT1 stimulates *Bmal1* and *Clock* transcription in the brain, by activating a positive feedback loop involving SIRT1, PGC-1α, and NAMPT. Aged mice showed decreased SIRT1, BMAL1 and PER2 levels in the SCN, resulting in a deregulated activity pattern and light entrainment. These effects were not observed in SCN SIRT1-overexpressing mice [156].

Decreases with Age resulting in deregulated activity pattern and light entrainment



The Cellular Clock and Metabolism Connected

Clock Controls NAMPT which controls NAD+ which is needed for key Metabolic Pathways and Repair

*This is **only one** example. 10-50% of the genes active in a cell are clock regulated*

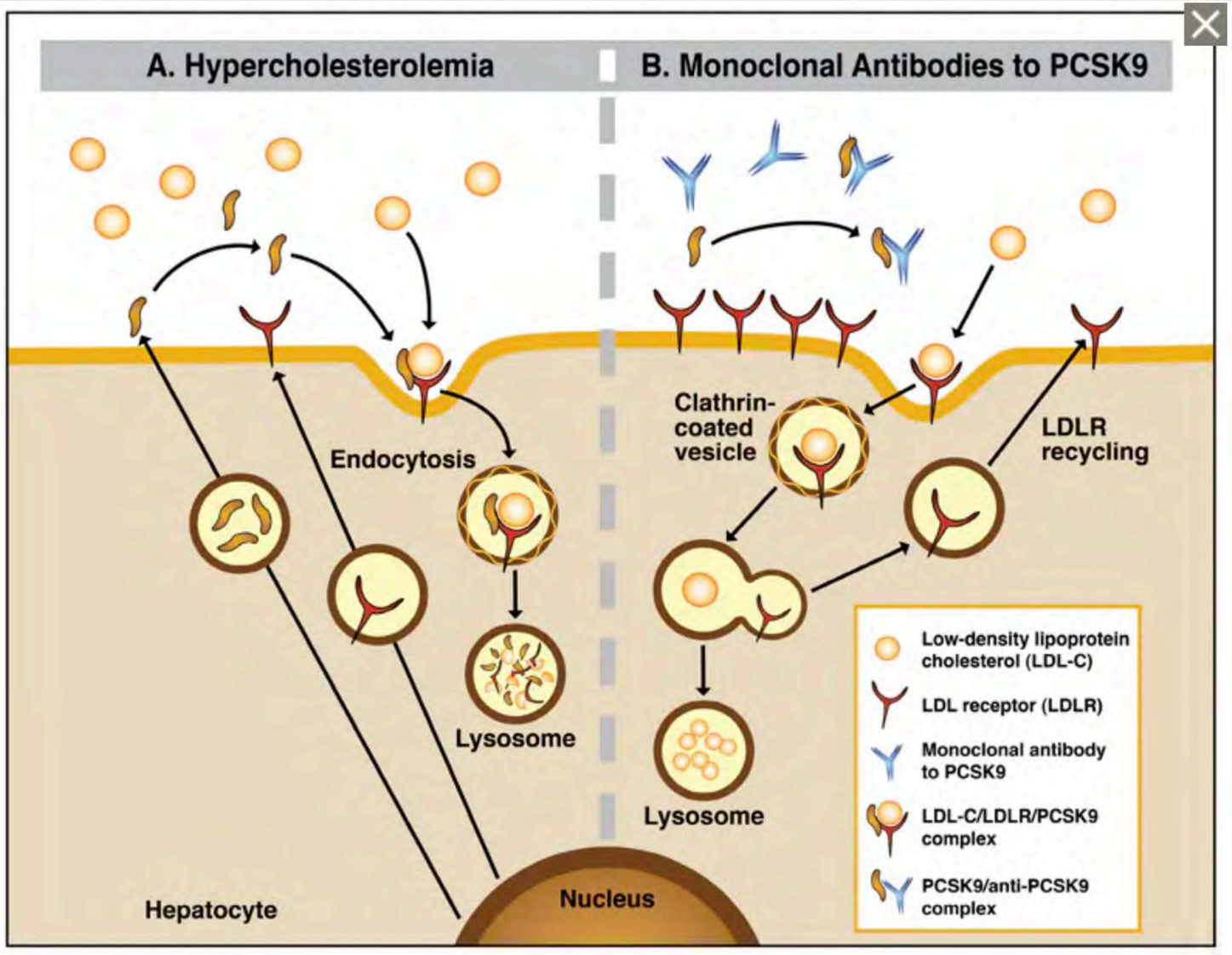
0156 Both Circadian Clock And Sleep Control Plasma Levels Of Pcsk9, The Main Regulator Of Plasma Ldl Cholesterol

Matthew P Butler, Saurabh S Thosar, Hagai Tavori, PhD, Melanie Rueger, David A Barr, Joshua R Miles, Sergio S Fazio, Steven A Shea

Sleep, Volume 42, Issue Supplement_1, April 2019, Pages A64–A65,
https://doi.org/10.1093/sleep/zsz067.155
Published: 12 April 2019

Conclusion

Both the endogenous circadian system and nocturnal sleep contribute to high levels of circulating PCSK9 in the morning. This regulation ties sleep and the circadian clock to the physiological regulation of PCSK9, and will have relevance for LDL-C regulation in shift workers or other conditions of circadian disruption or disrupted sleep. These findings increase our understanding of the physiological regulation of cholesterol homeostasis in healthy individuals and may also have relevance to patients with hypercholesterolemia.



PCSK9

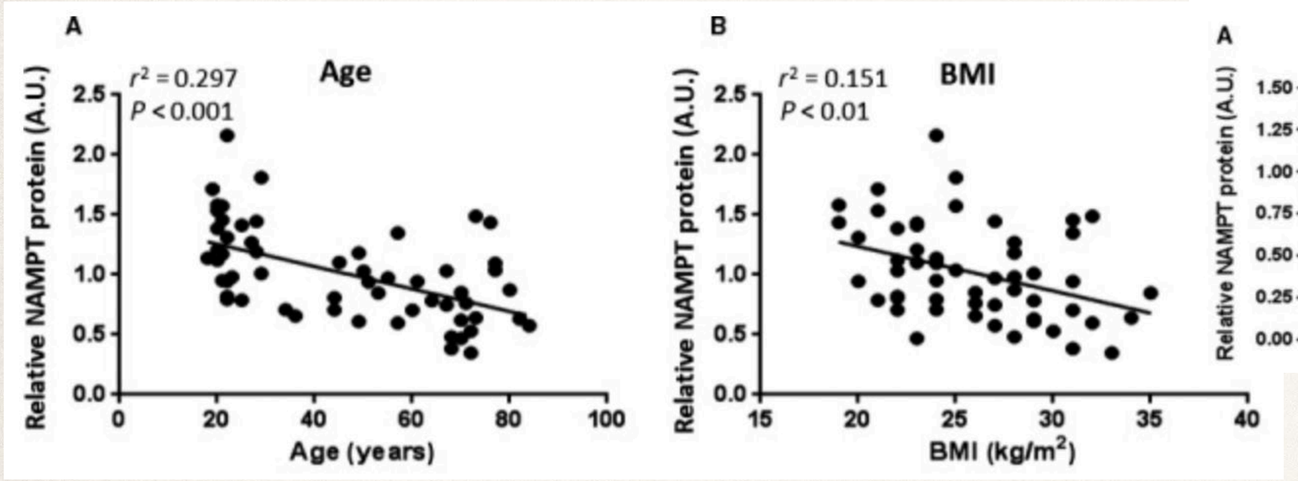
Clock Controlled and a Main Regulator of Lipid Profiles

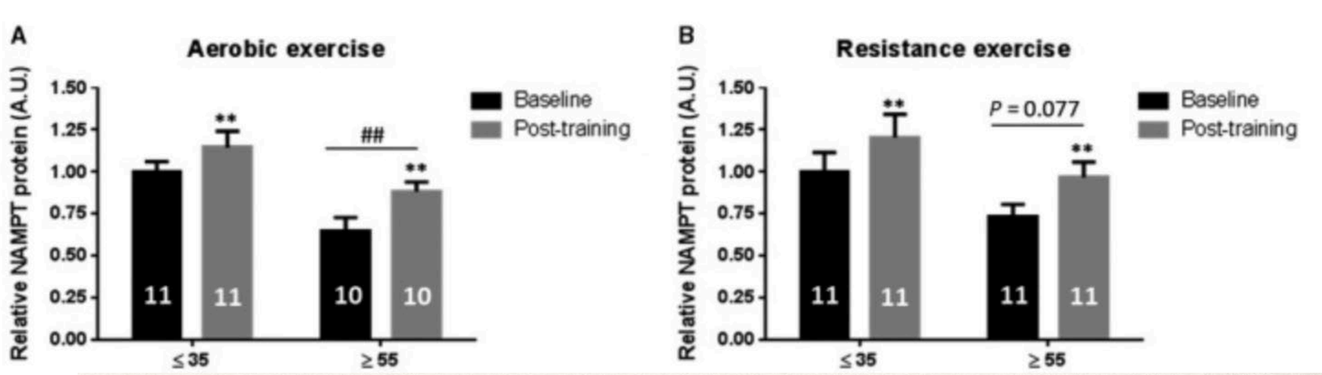
Main regulator of Plasma LDL levels. We seem to get too much of it when we are not sleeping well or in line with our natural rhythm, leading to higher LDL levels.

Physiol Rep. 2019 Jun; 7(12): e14139.
Published online 2019 Jun 17. doi: 10.14814/phy2.14139
PMCID: PMC6577427
PMID: 31207144

Aerobic and resistance exercise training reverses age-dependent decline in NAD^+ salvage capacity in human skeletal muscle

Roldan M. de Guia, [1,†] Marianne Agerholm, [1,8,†] Thomas S. Nielsen, [1,†] Leslie A. Consitt, [2] Ditte Søgaard, [3] Jørn W. Helge, [3] Steen Larsen, [3,4] Josef Brandauer, [5] Joseph A. Houmard, [6,7] and Jonas T. Treebak [1]





12wks of Exercise increases NAMPT

In Skeletal Muscle of Both Young and Old, Irrespective of Exercise Modality

Able to completely restore skeletal muscle NAMPT to levels observed in youth

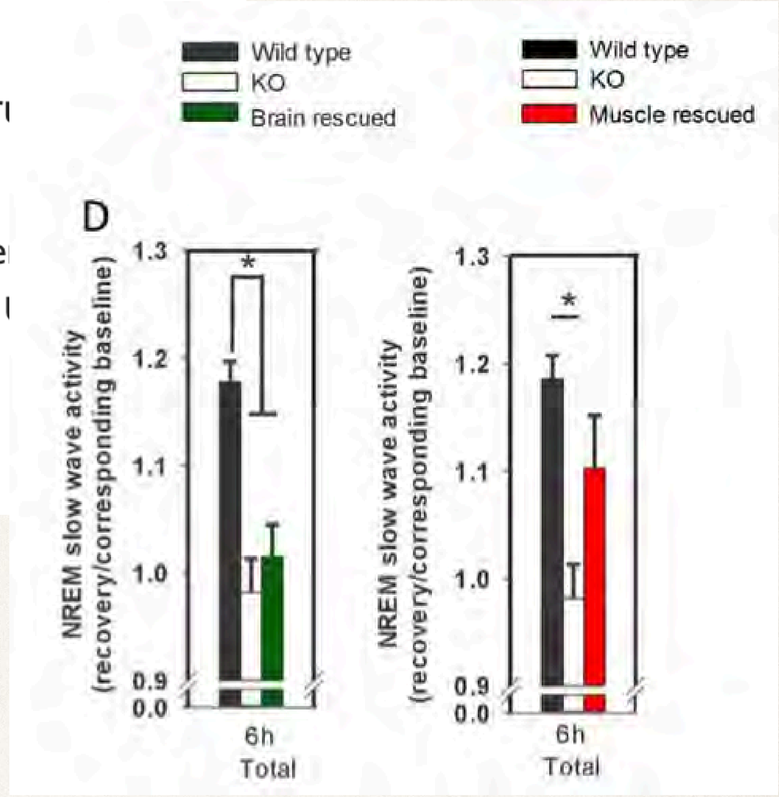
Bmal1 function in skeletal muscle regulates sleep

J Christopher Ehlen, Allison J Brager, Julie Baggs, Lennisha Pinckney, Cloe L Gray, Jason P DeBru
A Esser, Joseph S Takahashi, Ketema N Paul

Morehouse School of Medicine, United States; Walter Reed Army Institute of Res rch, United States; Unive
Florida, United States; Howard Hughes Medical Institute, University of Texas Sou tern Medical Center,
University of California, Los Angeles, United States

Jul 20, 2017 · https://doi.org/10.7554/eLife.26557

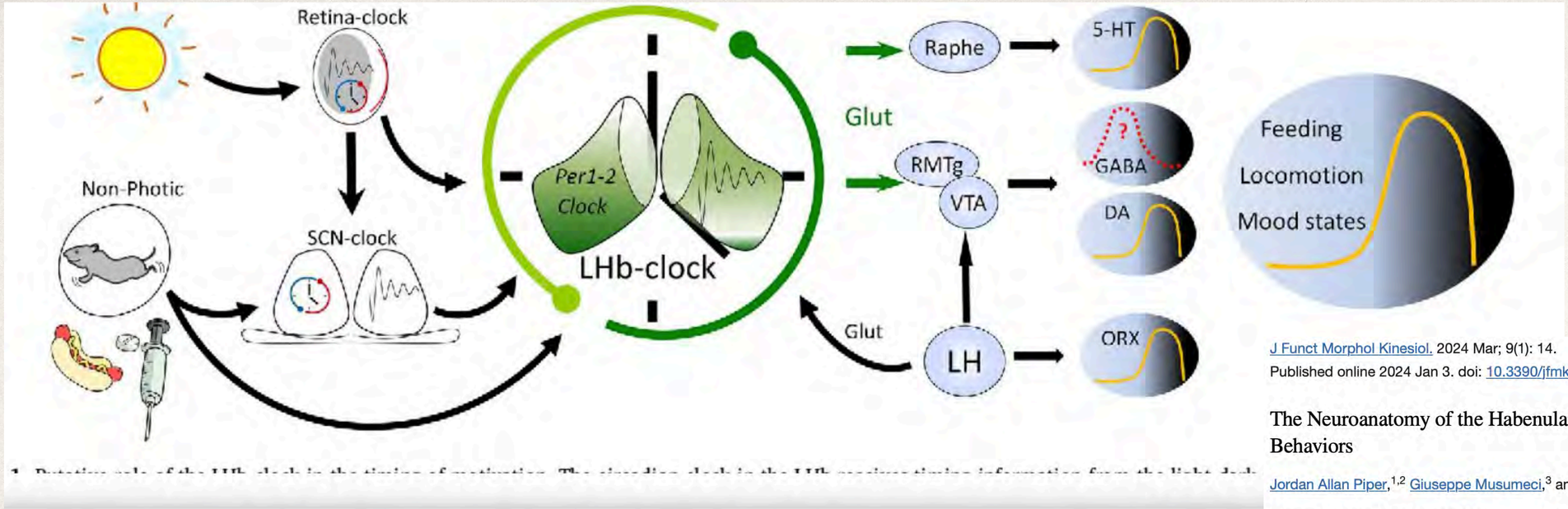
You don't need 8hrs of sleep
You need 16hrs of Labor



Skeletal BMAL1 appears to have greater control over NREM3 than Brain BMAL1

Connecting exercise to both the circadian and homeostatic sleep system

Helping us explain biochemically how exercise impacts the quality of sleep and thru that mental health



J Funct Morphol Kinesiol. 2024 Mar; 9(1): 14.
Published online 2024 Jan 3. doi: 10.3390/jfmk9010014
PMCID: PMC10801627
PMID: 38249091

The Neuroanatomy of the Habenular Complex and Its Role in the Regulation of Affective Behaviors

Jordan Allan Piper,[1,2] Giuseppe Musumeci,[3] and Alessandro Castorina[2,*]

Virginia Tancredi, Academic Editor

Fig. 1. Putative role of the LHb clock in the timing of motivation. The circadian clock in the LHb receives timing information from the light-dark cycle via the retina-LHb pathway and from the SCN clock. Moreover, other external non-photic cues (e.g., exercise, food, drugs) reset the SCN pacemaker and may have as well a setting effect on the LHb clock. The LHb cells (mainly glutamatergic) may set in time the neurochemistry (DA, 5-HT, GABA) of their principals targets (VTA, raphe, RMTg) and regulate the release of DA and 5-HT in the forebrain. However, whether GABA release from the RMTg and VTA shows a circadian profile is unknown. Thus, behaviors dependent on monoaminergic neurotransmission, which show circadian variability (locomotion, mood states) may in some way be modulated by the clock in the LHb closely coupling with the main clock in the SCN, and with the LH glutamatergic pathway (feeding). Collapse

ipRGCs Project directly into the Habenula

Habenula the “Anti Reward Center”

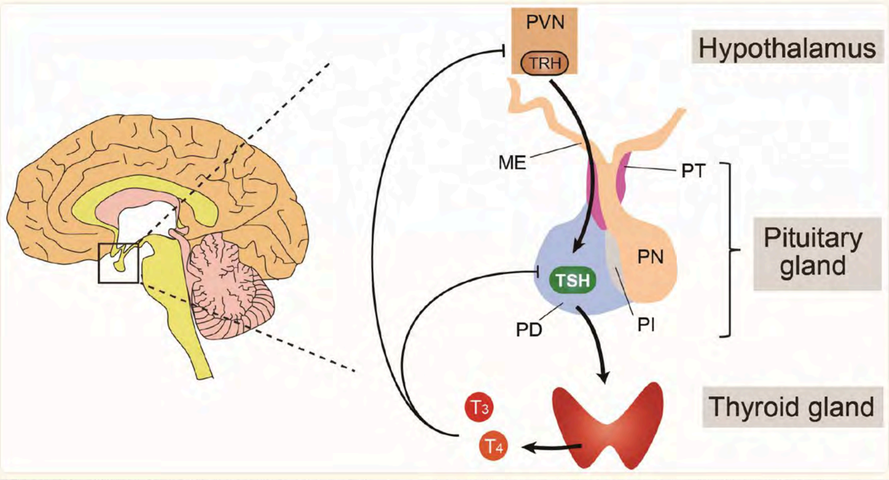
Clock Regulated conserved epithalamic structure regulating **mood, anxiety, and pain**

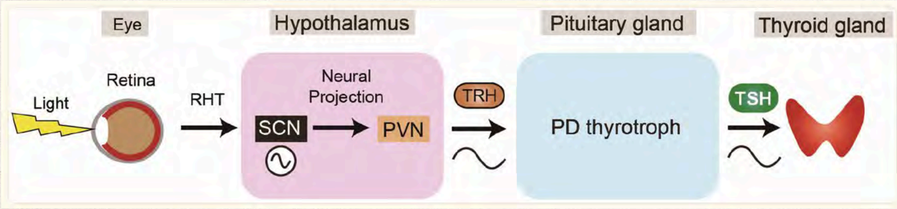
*Target for DBS, Ketamine, Propofol, Bright Light Therapy…. **Arrhythmic animals show an overall decrease in motivation***

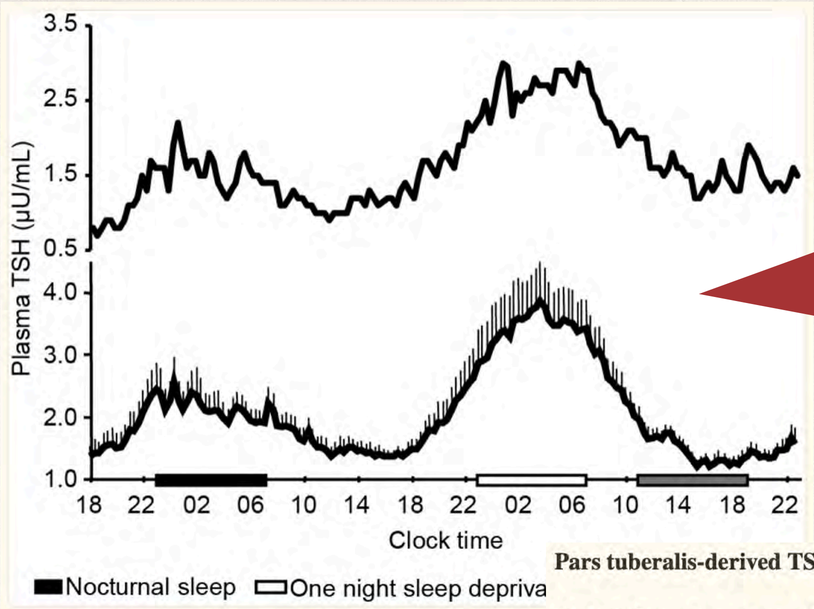
PMCID: PMC7288350 | NIHMSID: NIHMS1592694 | PMID: 31406343

Interconnection between circadian clocks and thyroid function

Keisuke Ikegami,[1] Samuel Refetoff,[2,3] Eve Van Cauter,[2] and Takashi Yoshimura[4,5,*]







Is it a waste of money to order thyroid functions when you know someone has circadian issues?

Safety and Efficacy of Low-Level Laser Therapy in Autoimmune Thyroiditis: Long-Term Follow-Up Study

Danilo Bianchini Höfling,[1] Maria Cristina Chavantes,[2] Carlos Alberto Buchpiguel,[3] Giovanni Guido Cerri,[3] Suemi Marui,[4] Paulo Campos Carneiro,[5] and Maria Cristina Chammas[1]

Misbalance of thyroid hormones after two weeks of exposure to artificial light at night in Eurasian perch *Perca fluviatilis*

Franziska Kupprat ✉, Werner Kloas, Angela Krüger, Claudia Schmalsch, Franz Hölker

Conservation Physiology, Volume 9, Issue 1, 2021, coaa124, https://doi.org/10.1093/conphys/coaa124
Published: 07 January 2021 **Article history ▾**

Pars tuberalis-derived TSH regulates seasonal thyroid hormone function.

Light information received by the eyes is transmitted to the pineal gland via the suprachiasmatic nuclei (SCN). Pineal melatonin secretion pattern reflects the length of nights and suppresses pars tuberalis-derived TSH expression. Long days increase production of pars tuberalis-derived TSH, which acts on ependymal cells in the hypothalamus to induce type 2 iodothyronine deiodinase (DIO2) expression through the TSH receptor–Gsα–cAMP signaling pathway. DIO2-induced thyroid hormone activation, through the generation of T_3 from T_4, transmits the springtime signal[128,132]. Pars distalis-derived TSH stimulates the thyroid gland. Pars tuberalis-derived TSH has tissue-specific *N*-glycans and forms macro-TSH complexes with immunoglobulin (IgG) and albumin in the circulation. The macro-TSH complexes are unable to stimulate the thyroid gland, and this feature prevents functional crosstalk between the two TSHs, thus preventing the production of seasonal thyroid gland overactivity[73].

Clock Control of HPT Axis

Thyroid involved in Metabolism, Heat Production, Development and Differentiation of Cells and Growth

There are **light controlled mechanisms** that decrease thyroid hormone production

Melatonin
Vasopressin
Adrenocorticotropin
Acetylcholine
Cortisol
Insulin
Ghrelin
Adiponectin
Leptin
Growth Hormone

Gonadal hormone functions

Testosterone:
- Improving the primary sex organs
- Improving semen
- Semen production
- Achieving maturity of the penis and testicles
- Secondary sex characteristics
- Improving Nerve Tissue
- Acne
- Increase metabolism

Estrogen:
- Increased fat
- Stimulation of endometrial growth
- Enhancing the uterus
- Increased vaginal lubrication
- Increased thickness of the vaginal wall
- Increasing bone structure
- Women's secondary sex characteristics

Progesterone:
- Increase body temperature
- Increase sex drive
- Maintains healthy libido
- Maintains the function of placenta
- Natural diuretic
- Acts as natural antidepressant
- Inhibits breast cancer and endometrial cancer

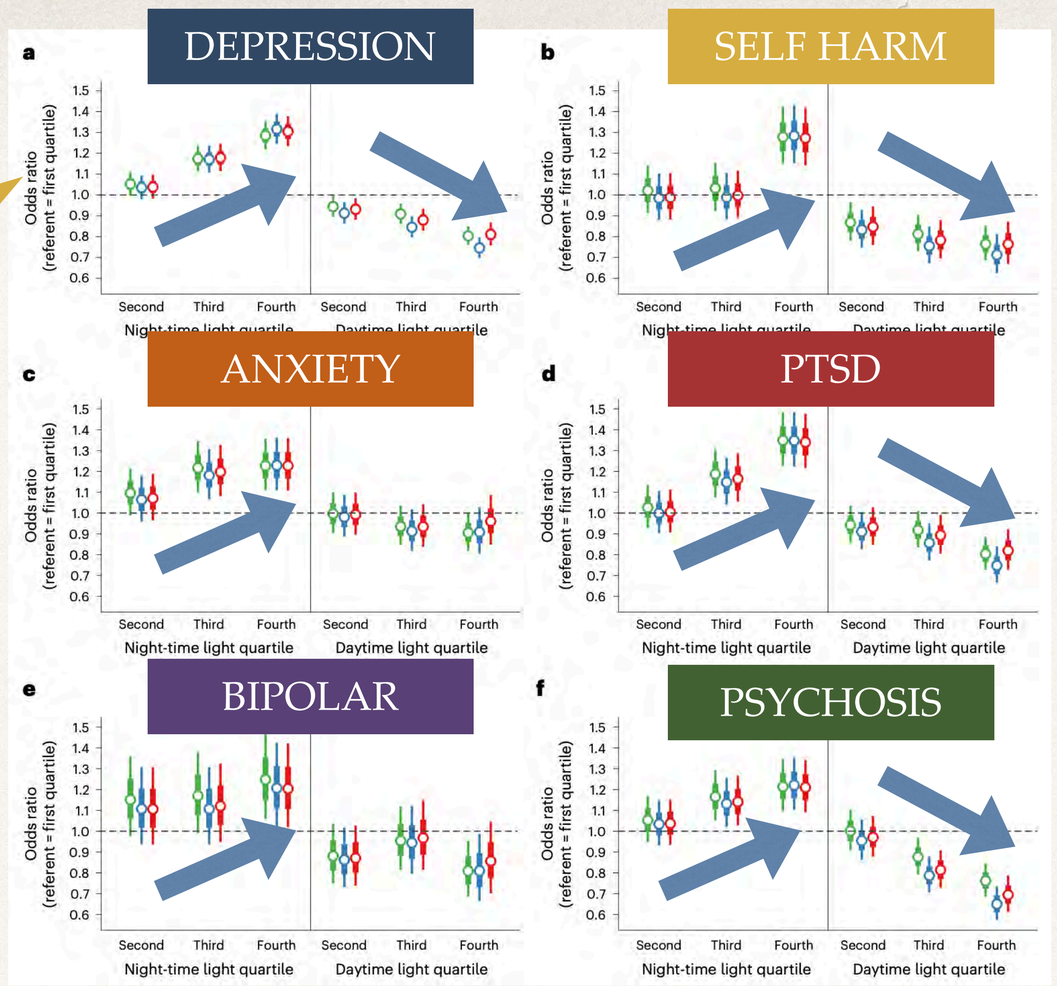
Testosterone Deficiency is associated with poor sleep

Other Clock Controlled Hormones

Does anyone know a hormone that is not Clock Controlled?

Technically optimizing anyone of these requires good sleep and good sleep habits.

INDEPENDENT of
Demographics
Physical Activity
Employment
Shiftwork
Sleep Quality



Article
https://doi.org/10.1038/s44220-023-00135-8

Day and night light exposure are associated with psychiatric disorders: an objective light study in >85,000 people

Light Exposure and Risk of Mental Health Disease

As Light Exposure at Night goes up so does risk of Mental Health Disease

As Light Exposure in the Day goes down the risk of Mental Health Disease Rises

Lithium a main treatment for the cyclic disease of Bipolar Disorder lengthens the clock period

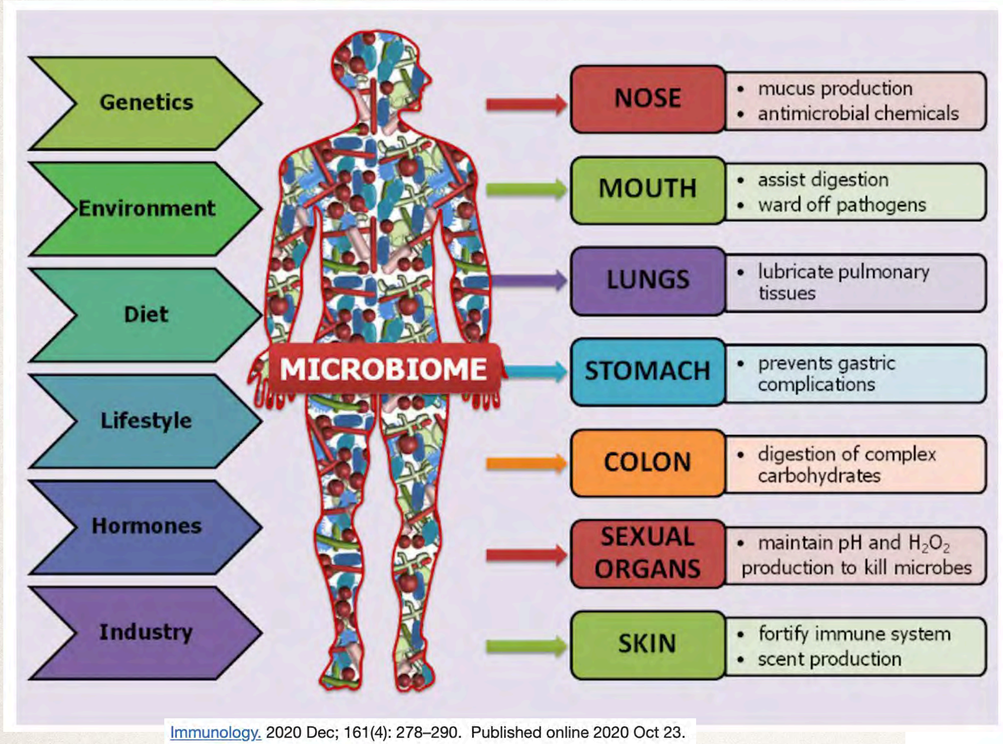
Employment is associated with greater circadian stability and appears to work to decrease health risks

Probiotics have shown beneficial effects on performance, sleepiness, **mood** in the setting of circadian misalignment

Circadian Mental Health

We know poor sleep leads to viewing the world and our self more negatively, affects motivation, energy levels, concentration, and appetite.

Disturbed Sleep Predicts Next Day Suicidality and just about every mental health disorder has a sleep related link

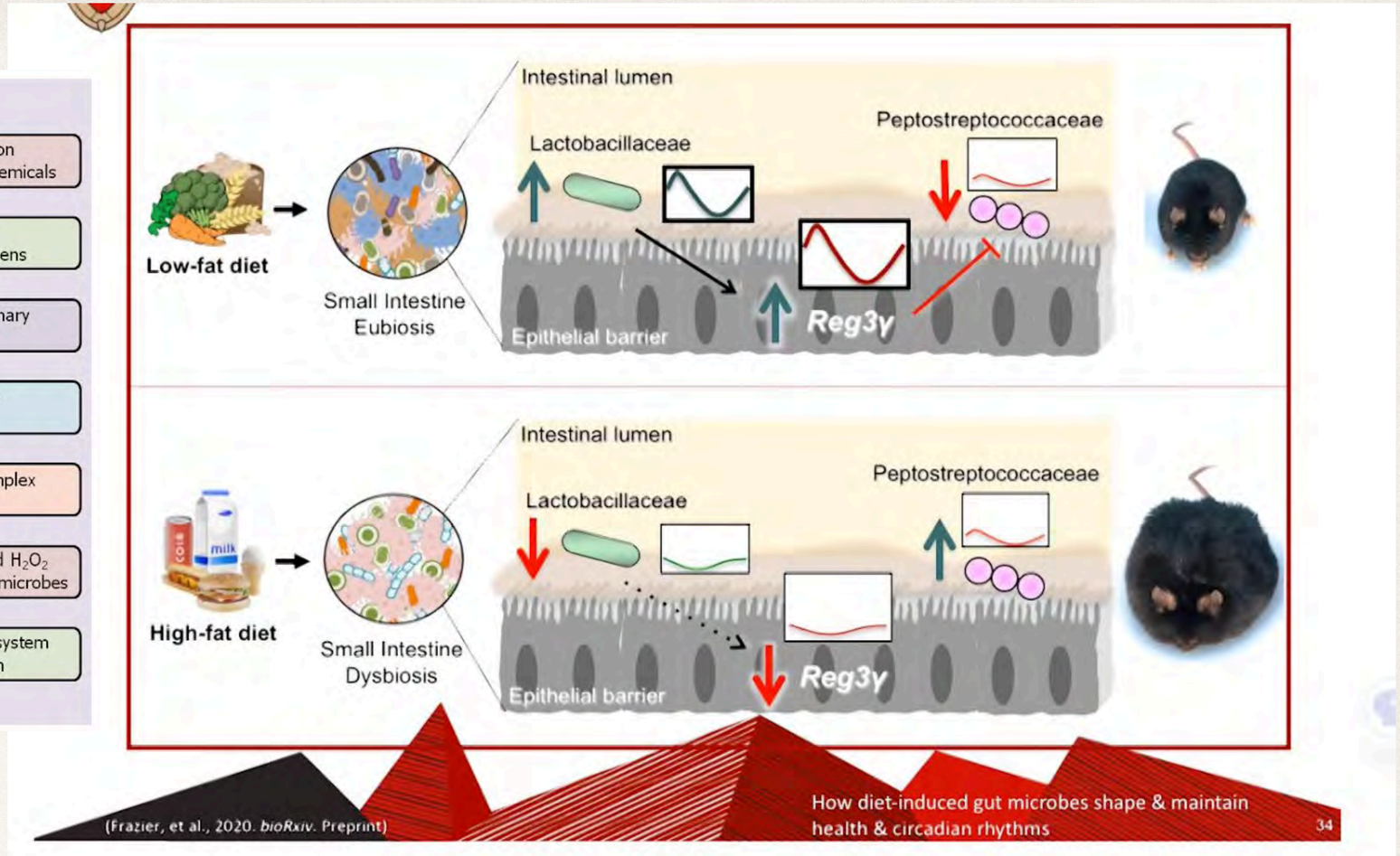


Immunology. 2020 Dec; 161(4): 278–290. Published online 2020 Oct 23.
doi: 10.1111/imm.13278

PMCID: PMC7692254 | PMID: 33090484

Crosstalk between circadian rhythms and the microbiota

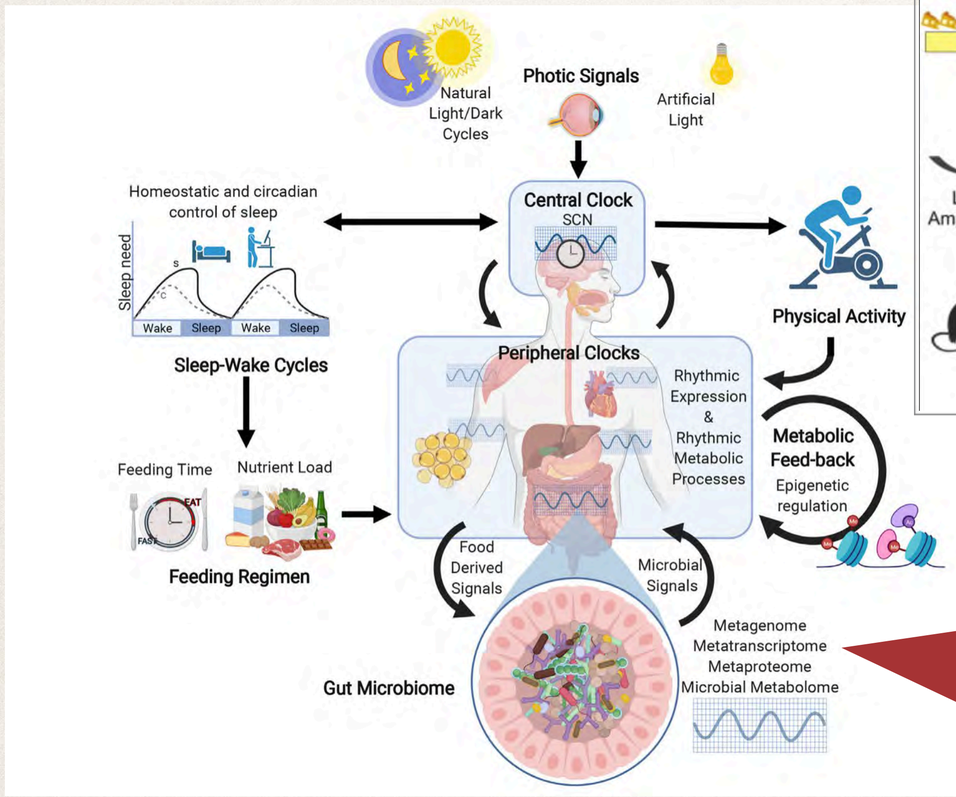
James Alexander Pearson,[1,2] Florence Susan Wong,[1] and Li Wen[2]

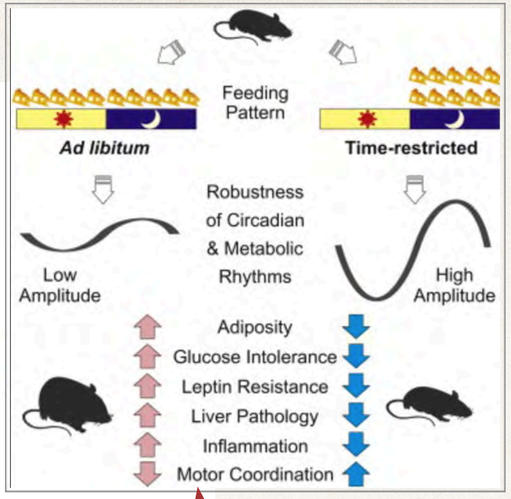


Diet, Microbes, Rhythm, Immunity, and Obesity

Microbiota can transfer metabolic dysfunction and health from one host to another

Microbiotic composition can modulate vaccine efficacy





Timing Matters

Decreased TST Higher carb Intake and Higher Insulin Resistance

Improved Sleep Better glucose metabolism

Later Chronotype Higher HgbA1C

- Later Eaters Higher Glucose Responses to the Same Meal

More Circadian Variability Higher BMI, Increased Calories

Prebiotic in AD Improved Circadian Timing of Sleep and Memory Retention

Cognitive Performance Worse in Chronic Caffeine Users

Increased Protein and Fiber Increased Sleep

Increased Carbs Decreased Sleep and Increased Fatigue

Sleep and the Gut

More Circadian Variability More Insulin Resistance, **higher BMI**

Circadian Misalignment predicts sugar consumption

Carbs tend to worsen sleep and create fatigue, Worse Sleep leads to higher carb intake and more insulin resistance

JIM Journal of Internal Medicine
Founded in 1863

Review | Open Access

The Circadian Syndrome: is the Metabolic Syndrome and much more!

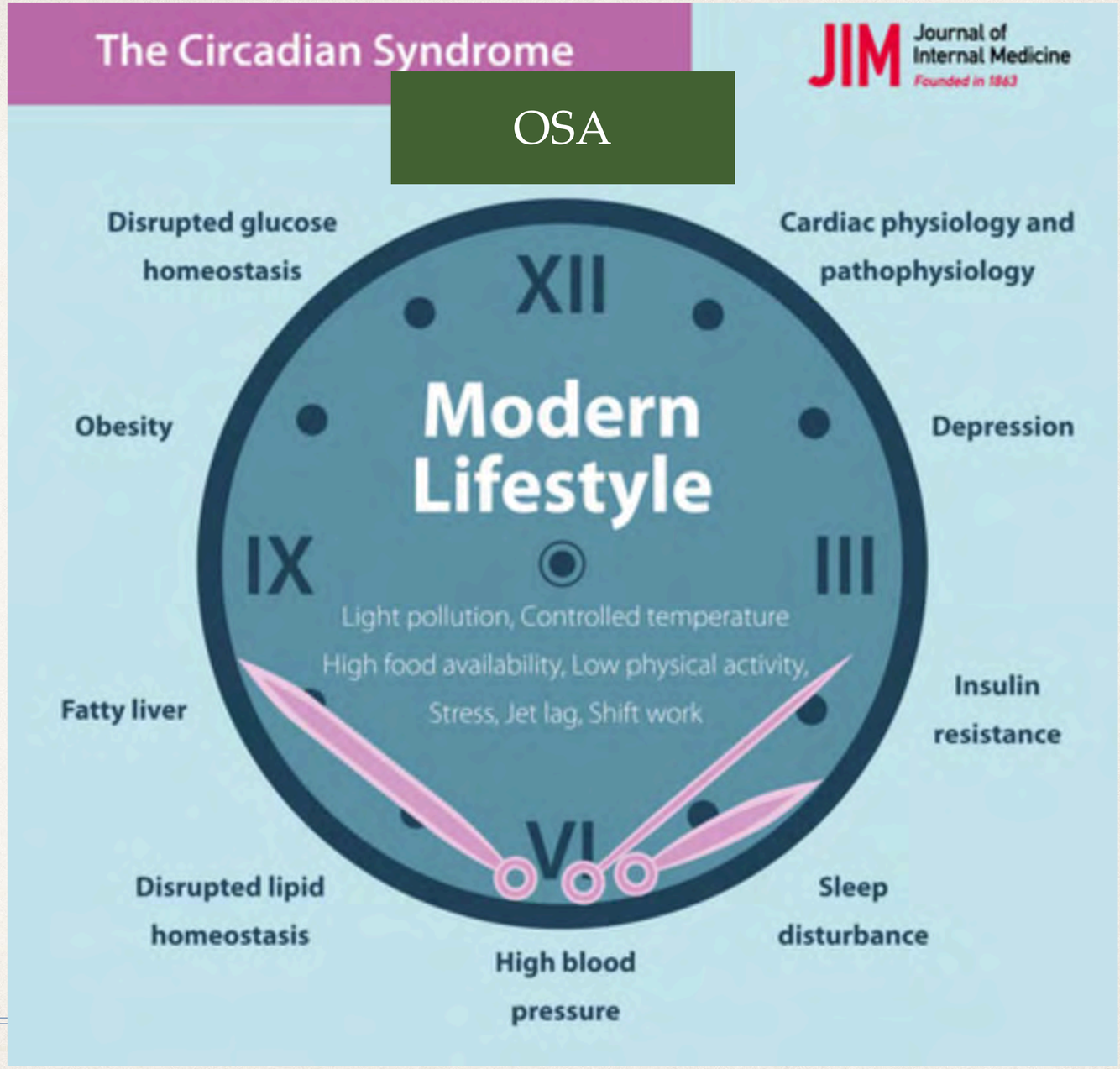
P. Zimmet, K. G. M. M. Alberti, N. Stern, C. Bilu, A. El-Osta, H. Einat, N. Kronfeld-Schor

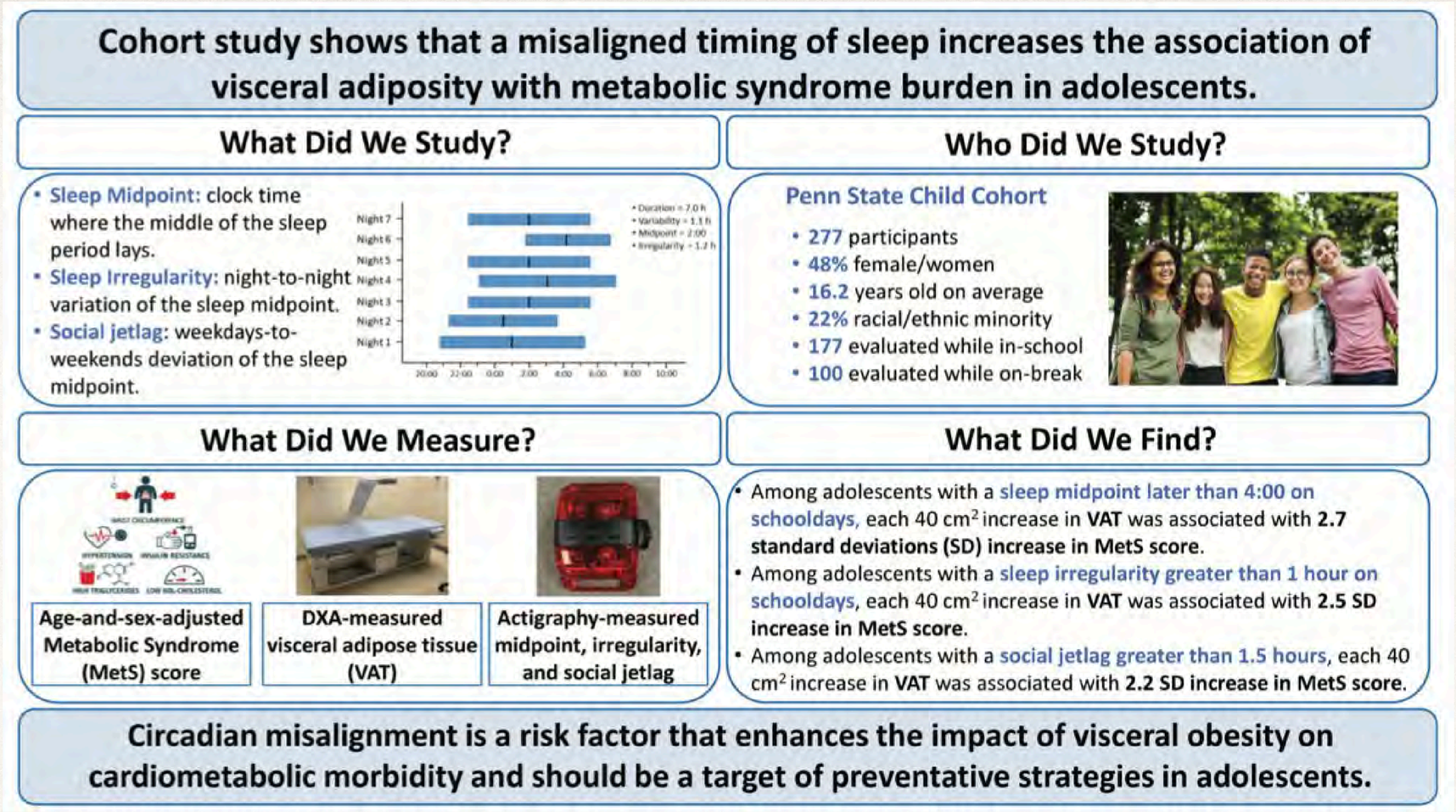
First published: 13 May 2019 | https://doi.org/10.1111/joim.12924 | Citations: 146

Circadian Syndrome

Metabolic Syndrome has gotten a Rename

If I were in charge of this paper I would have added OSA





Circadian Misalignment RF for Visceral Obesity

Morales-Ghinaglia and Fernandez-Mendoza et al

Study in Adolescents

The Impact of Screen Time on Sleep Patterns in School-Aged Children: A Cross-Sectional Analysis

Chandra Sekhar G [1], Haarika V [1], Kedarnath Reddy Tumati [1], Uma Mahesh Ramisetty [1]

Affiliations + expand

PMID: 38425328 PMCID: PMC10903530 DOI: 10.7759/cureus.55229

VARIABLE	<1HR SCREEN TIME	>3HRS SCREEN TIME
GRADES	A+ - A	B
SLEEP EFFICIENCY	90%	75%
DREAM RECALL	70%	30%
NOCTURNAL AWAKENINGS	0.5	1.5
DAYTIME SLEEPINESS	20%	60%
PHYSICAL ACTIVITY	60min/day	30min/day
EXTRACURRICULAR ACTIVITIES	5hrs/week	2hrs/week
WEEKEND SLEEP VARIABILITY	0.8hrs	1.5hrs
CIRCADIAN DISTURBANCE	5%	20%
SCREEN FREE BEDROOM	85%	30%
PARENT INVOLVED AT BEDTIME	90%	40%

Screen Time and Pediatric Circadian Health

Study of 1,000 kids age 6-14yo using wearable sleep monitors and completing sleep diaries

Less Screens was associated with better grades, better and more sleep, more physical activities and involvement in extracurriculars, less circadian disruption

Shiftwork	Method of staffing in which different employees work at different times during the day, including times outside the classic 800–1800 hours. The "shift" is the unit of work time scheduled per day.
Fixed shift schedule	A method of scheduling shiftwork in which the individual always works the same hours each day.
Rotating shift schedule	A method of scheduling shiftwork in which the individual periodically changes the shift worked.
Shift rotation rate	A measure of the number of consecutive days an individual works before changing shifts.
Forward rotation	A change in shift to one later in the day, or clockwise, also known as a "delay shift." The most circadian-friendly method.
Backward rotation	A change in shift to one earlier in the day, or counter-clockwise, also known as an "advance shift." The least circadian-friendly method.
Circadian rhythms	Periodic patterns of physiologic systems (from Latin, "about a day"). In humans, these rhythms have a natural 25-hour cycle, but external cues keep them synchronized to a 24-hour period.
Zeitgebers	Environmental time-cues that modulate circadian rhythms, such as the light/dark cycle (from German, "time-givers"). Without these cues, human rhythms migrate to a 25-hour schedule.
Dysynchrony syndrome	A constellation of effects and symptoms due to a disharmony of circadian rhythms induced by conflicting *zeitgebers* (such as a work phase shift). It manifests as sleep loss, malaise, GI symptoms, irritability and reduced performance.
Jet lag	A circadian dysynchrony syndrome resulting from transmeridian travel.
Partial vs. complete sleep loss	Shiftwork disrupts sleep, leading to partial sleep loss daily, and a cumulative sleep debt. Complete sleep loss involves skipping one entire sleep period, as in staying up all night.
Shiftwork syndrome	A dysynchrony syndrome due to chronic shiftwork. It is characterized by a constellation of problems including chronic fatigue, GI symptoms, alcohol or drug abuse, higher rates of accidents, mood disturbances, and interpersonal relationship disturbances.

Light at Night

Obesity
HTN
DM
Causes more insulin secretion to maintain glucose levels
Increased HR
More Cancer

Shiftwork

Overexpression of BMAL1 at the wrong circadian timing results in inhibition of mTOR pathways and reduces oligodendrocyte myelination

PMID: 38241675

Shiftwork changes our metabolic responses to meals and has been shown to increase diastolic blood pressure

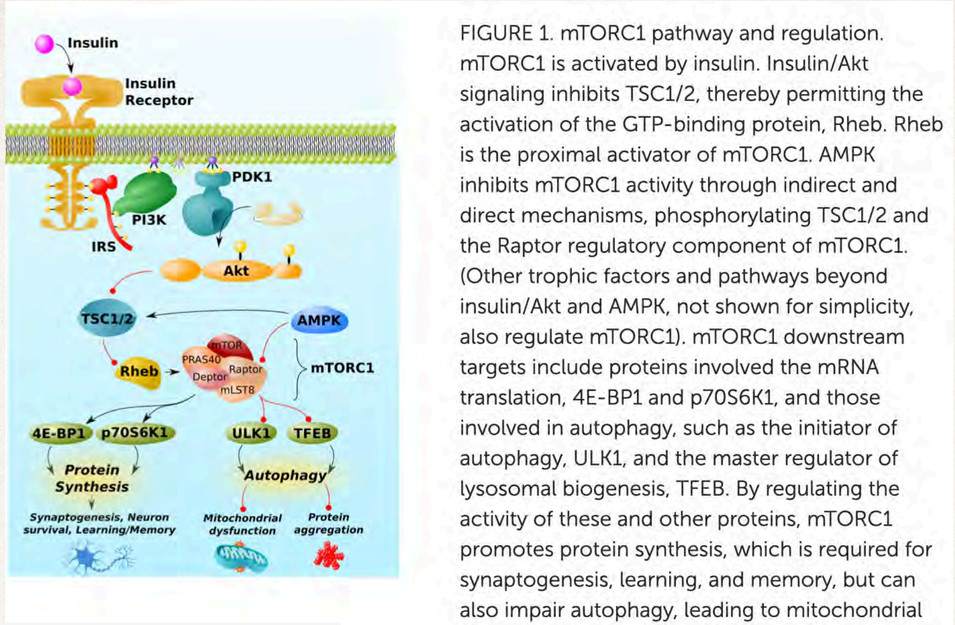


FIGURE 1. mTORC1 pathway and regulation. mTORC1 is activated by insulin. Insulin/Akt signaling inhibits TSC1/2, thereby permitting the activation of the GTP-binding protein, Rheb. Rheb is the proximal activator of mTORC1. AMPK inhibits mTORC1 activity through indirect and direct mechanisms, phosphorylating TSC1/2 and the Raptor regulatory component of mTORC1. (Other trophic factors and pathways beyond insulin/Akt and AMPK, not shown for simplicity, also regulate mTORC1). mTORC1 downstream targets include proteins involved the mRNA translation, 4E-BP1 and p70S6K1, and those involved in autophagy, such as the initiator of autophagy, ULK1, and the master regulator of lysosomal biogenesis, TFEB. By regulating the activity of these and other proteins, mTORC1 promotes protein synthesis, which is required for synaptogenesis, learning, and memory, but can also impair autophagy, leading to mitochondrial dysfunction and neurotoxic protein aggregation (Aβ, phospho-tau, α-synuclein, etc.). Black arrows and red lines respectively represent positive and negative regulation.

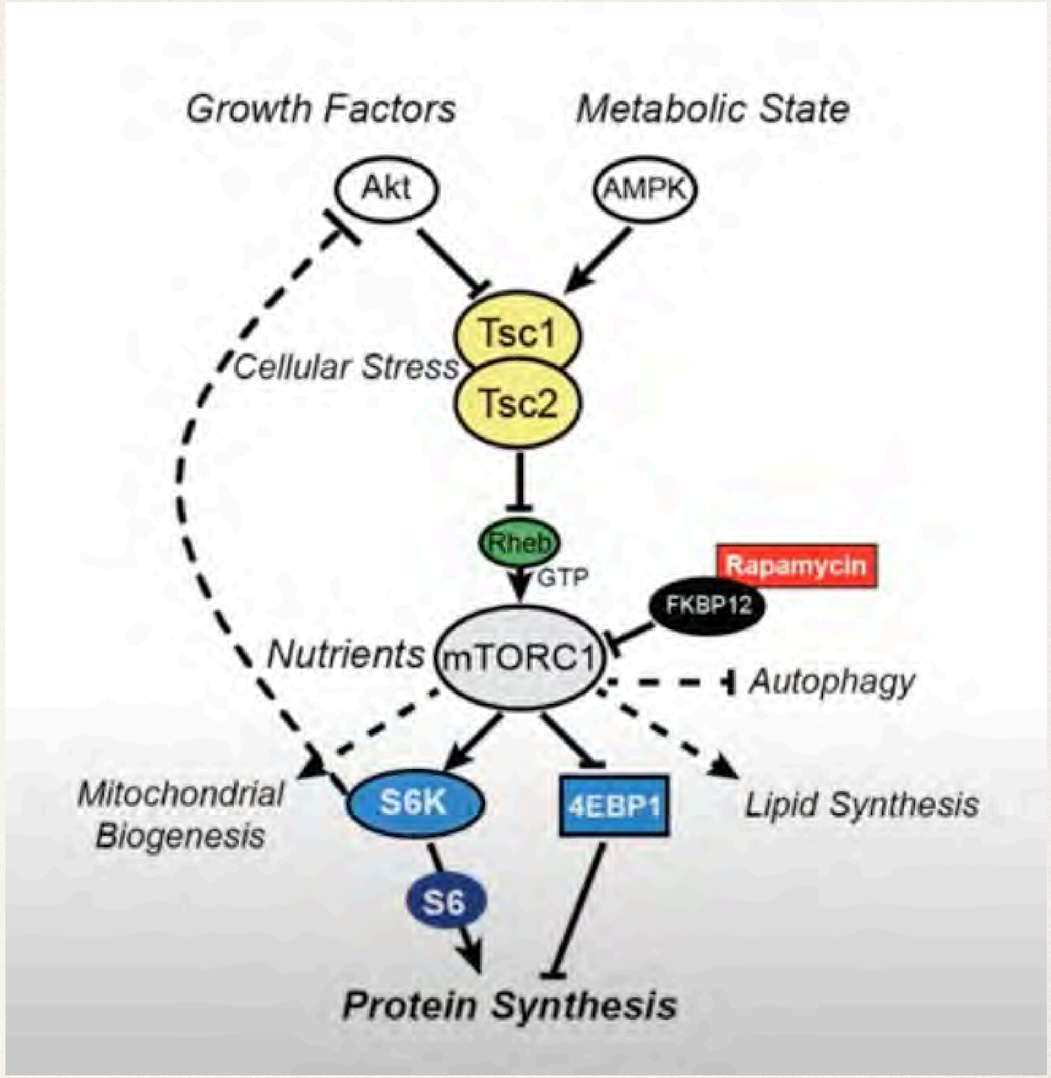
PERSPECTIVE article

Front. Neurosci., 29 July 2020
Sec. Neurodegeneration
Volume 14 - 2020 | https://doi.org/10.3389/fnins.2020.00775

This article is part of the Research Topic
Metabolism in Alzheimer's Disease
View all 11 Articles >

mTOR Mysteries: Nuances and Questions About the Mechanistic Target of Rapamycin in Neurodegeneration

Nicholas G. Norwitz[1*] and Henry Querfurth[2]



mTOR (agent of aging)

Mechanistic Target of Rapamycin (senses nutrient, oxygen, and energy levels -acting as a central regulator of metabolism)

Regulates Cell Growth, Proliferation, Motility, Survival, Protein Synthesis, Autophagy, and Transcription working thru Insulin Receptors and Insulin-like Growth Factor 1 it prevents Autophagy

The trilateral interactions between mammalian target of rapamycin (mTOR) signaling, the circadian clock, and psychiatric disorders: an emerging model

Rubal Singla, Abhishek Mishra & Ruifeng Cao

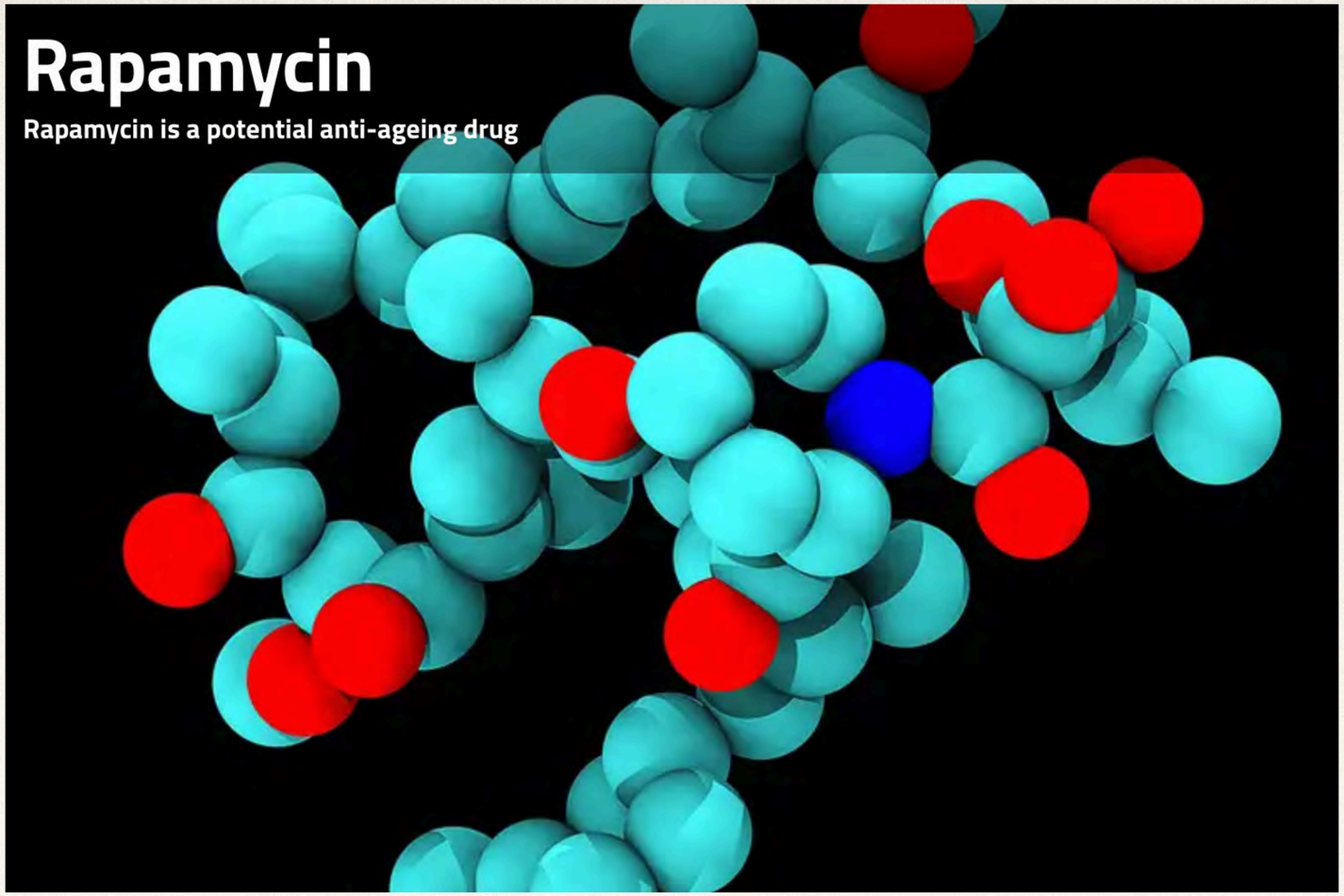
Translational Psychiatry **12**, Article number: 355 (2022) | Cite this article

Circadian (~24 h) rhythms in physiology and behavior are evolutionarily conserved and found in almost all living organisms. The rhythms are endogenously driven by daily oscillatory activities of so-called "clock genes/proteins", which are widely distributed throughout the mammalian brain. Mammalian (mechanistic) target of rapamycin (mTOR) signaling is a fundamental intracellular signal transduction cascade that controls important neuronal processes including neurodevelopment, synaptic plasticity, metabolism, and aging. Dysregulation of the mTOR pathway is associated with psychiatric disorders including autism spectrum disorders (ASD) and mood disorders (MD), in which patients often exhibit disrupted daily physiological rhythms and abnormal circadian gene expression in the brain. Recent work has found that the activities of mTOR signaling are temporally controlled by the circadian clock and exhibit robust circadian oscillations in multiple systems. In the meantime, mTOR signaling regulates fundamental properties of the central and peripheral circadian clocks,

mTOR controlled by the clock

Biochemically Connecting Circadian Amplitude to Mental Health

You need to run its pathways to adequately process sugar, those pathways appear to be impacted in a deleterious way when we are exposed to light at night or have circadian misalignment



Rapamycin (agent of youth)

Inhibits mTOR1 and induces Autophagy (both helpful to prevent aging)

Found to reliably increase lifespan

Circadian Misalignment predicts sugar consumption

Sugar

If great sleep and hormetic experiences are the heroes of longevity, sugar might be biggest villain around

---

It activates mTOR and prevents autophagy.

7a-3p TRE

weight loss
improved glucose levels
decreased caloric intake
reduced fatigue
increased energy levels
improved leptin/ghrelin

8a-6p TRE in DM

weight loss
improved glucose levels
improved triglycerides
and LDL

LATE TRE

MAY WORSEN CARDIAC HEALTH AND INCREASE HUNGER

Nutrients. 2019 Jun; 11(6): 1234.
Published online 2019 May 30. doi: 10.3390/nu11061234
PMCID: PMC6627766
PMID: 31151228

Early Time-Restricted Feeding Improves 24-Hour Glucose Levels and Affects Markers of the Circadian Clock, Aging, and Autophagy in Humans

Humaira Jamshed,[1] Robbie A. Beyl,[2] Deborah L. Della Manna,[3] Eddy S. Yang,[3] Eric Ravussin,[4] and Courtney M. Peterson[1,*]

Eating window 8am-2pm

Time-restricted feeding regulates molecular mechanisms with involvement of circadian rhythm to prevent metabolic diseases

Falak Zeb [1], Xiaoyue Wu [2], Sanyia Fatima [3], Muhammad Haidar Zaman [4], Shahbaz Ali Khan [5], Mahpara Safdar [6], Iftikhar Alam [7], Qing Feng [2]

Affiliations + expand

PMID: 33930788 DOI: 10.1016/j.nut.2021.111244

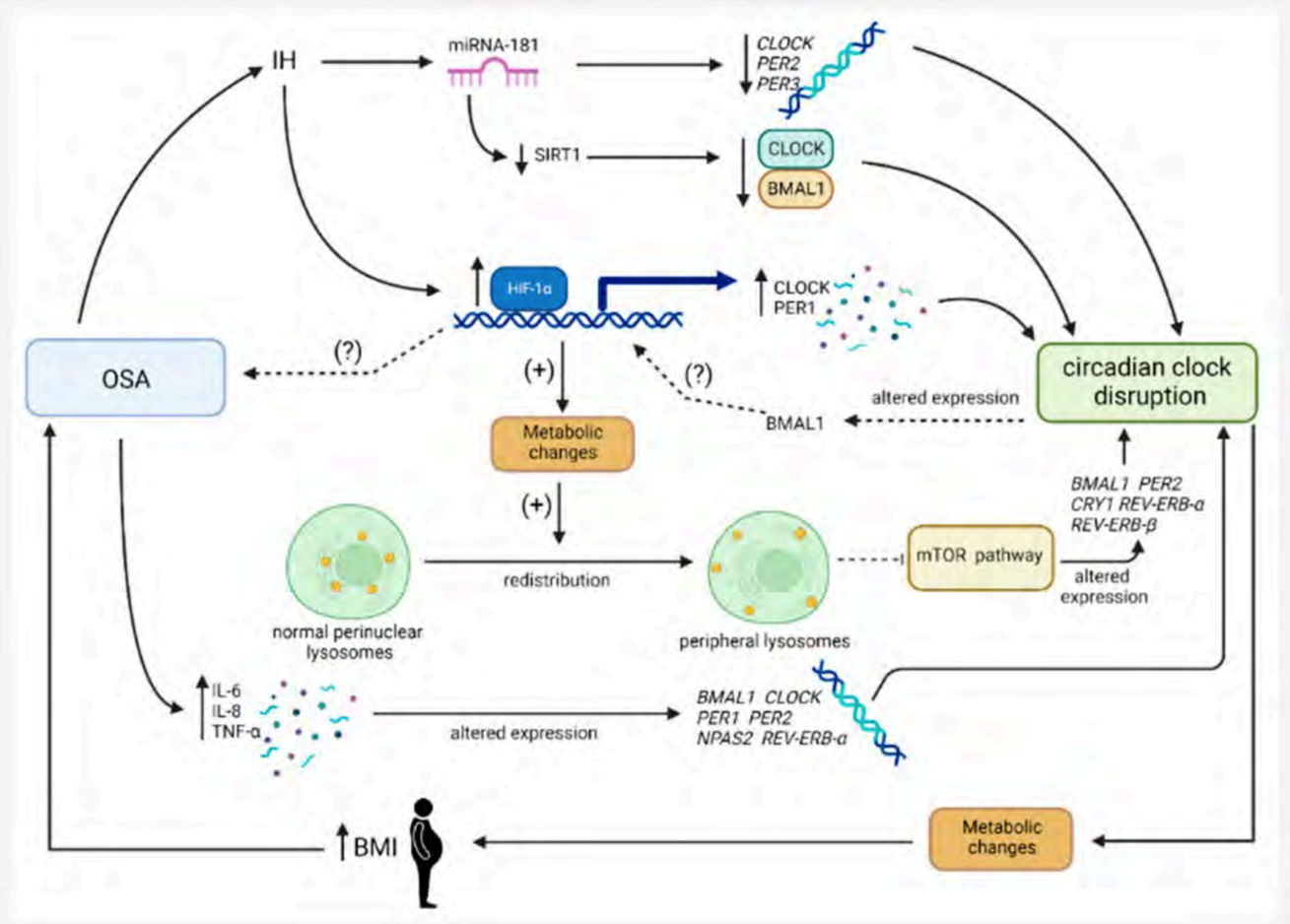
Abstract

Lifestyle and genetic perturbation of circadian rhythm can trigger the incidence and severity of metabolic diseases. Time-restricted feeding (TRF) regulates the circadian rhythm of food intake that protects against metabolic disorders induced by adverse nutrient intake. TRF also executes host metabolism from nutrient availability to optimize nutrient utilization. Circadian clock and nutrient-sensing pathways coordinate to regulate metabolic health through the feeding/fasting cycle. Concurrently, TRF imposes diurnal rhythm in nutrient utilization, thereby preserving cellular homeostasis. However, modulation of daily feeding and fasting periods calibrates the circadian clock, which protects against the lethal effects of nutrient imbalance on metabolism. Therefore, TRF also improves and restores metabolic rhythms that ultimately lead to better fitness by reversing the alteration in genotype-specific gene expression. The aim of this review was to summarize that TRF is an emerging dietary approach that maintains robust circadian rhythms in support of a steady daily feeding and fasting cycle. TRF also encourages the coordination between circadian clock components and nutrient-sensing pathways via molecular effectors that exert a protective role in the prevention of metabolic diseases.

Time Restricted Eating (TRE)

When we turn on certain biochemical pathways and for how long those pathways are working appear to be very important to our metabolic health

8am-6pm TRE increased TST by almost 1hr, reduced Leptin levels, promoted increased fat utilization



OSA Circadian Bidirectional Link

CLOCK, PER2, PER3, SIRT1 impacted by OSA thru miRNA-181 which then lead to metabolic changes that increase weight

OSA often produces phasic sleep *which leads to inconsistent timing of sleep, impacting the circadian system both thru flight or fight and inconsistency of timing*

PMCID: PMC8476957 | PMID: 34595127

Circadian Clock Regulates Inflammation and the Development of Neurodegeneration

Xiao-Lan Wang [1,†] and Lianjian Li [2,3,*]

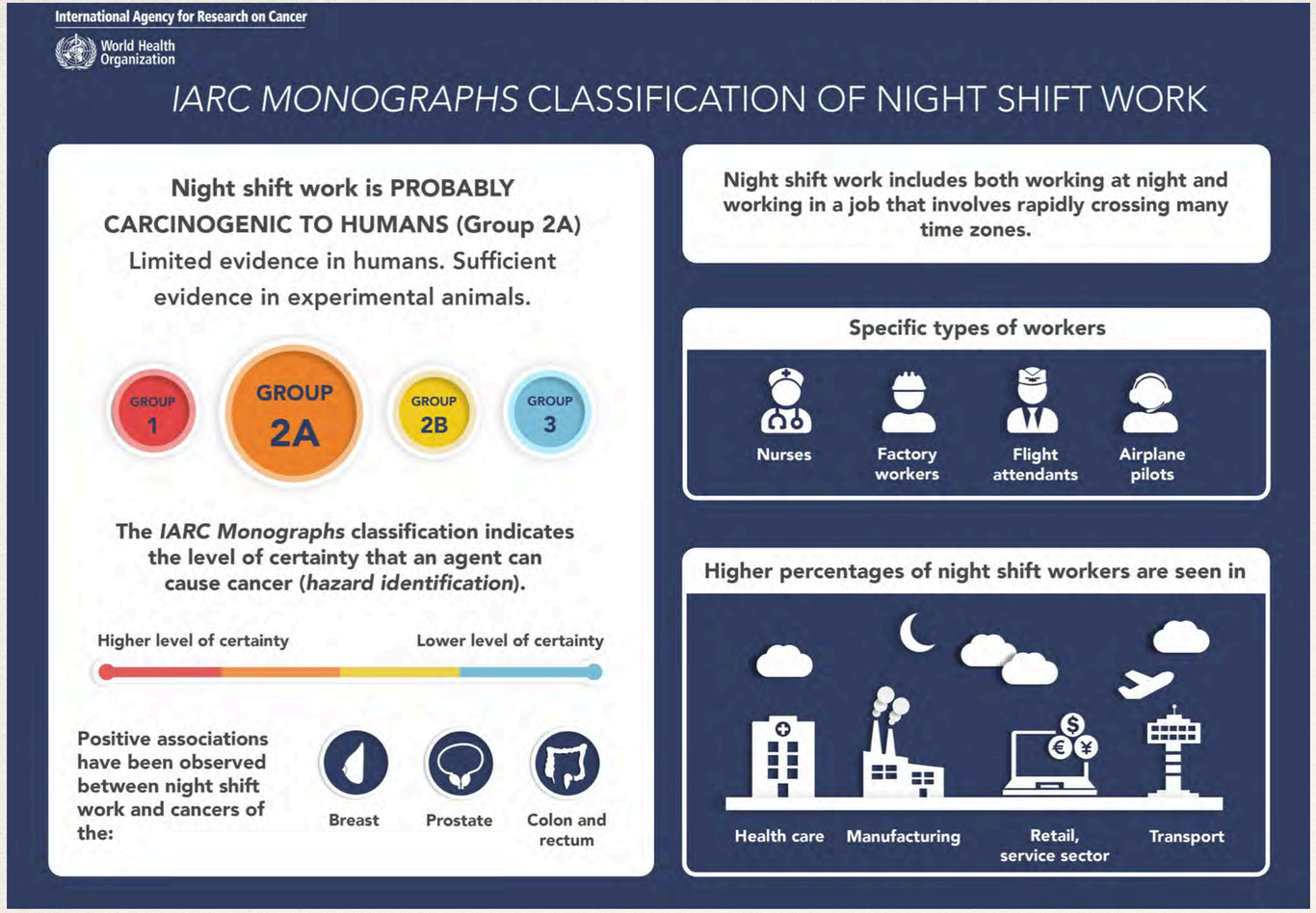
Circadian Control of
Trafficking of Immune Cells
Pathogen Recognition
Phagocytic Capacity
Secretion of
Inflammatory Cytokines
Chemokines
and Complement Factors

40lux nighttime exposure impaired daytime function and increased CRP values by 40%

Circadian Influence on Inflammation/Immunity

Mortality caused by Lethal Bacteria varies according to time of the infection

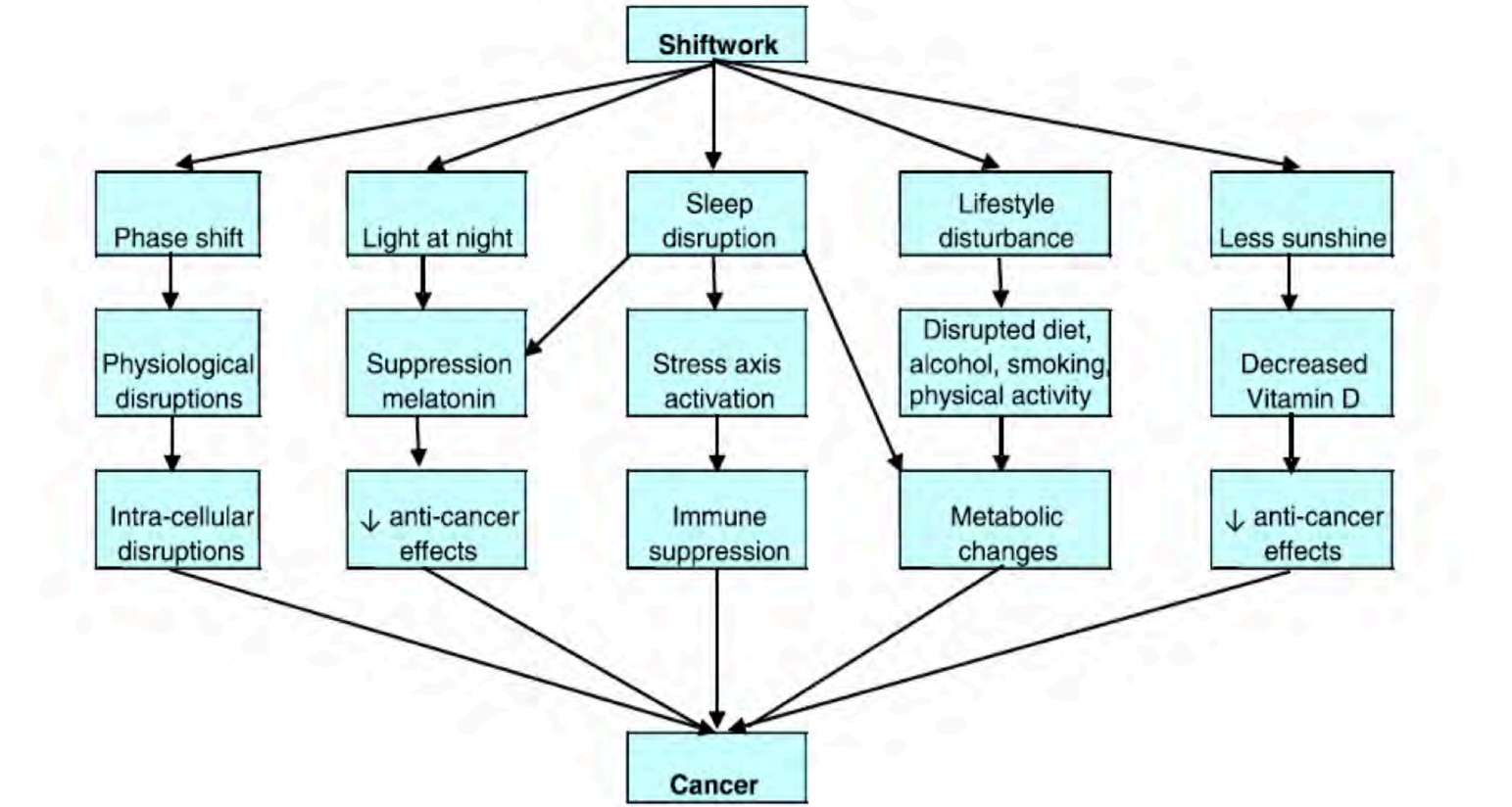
Affecting the immune system in many ways chronic circadian dysregluation is thought to be a main pathway to development of both Dementia and Cancer



Light and Cancer

Equivalent to Formaldehyde and Red Meat

Not thought to be as dangerous as processed meats or alcohol

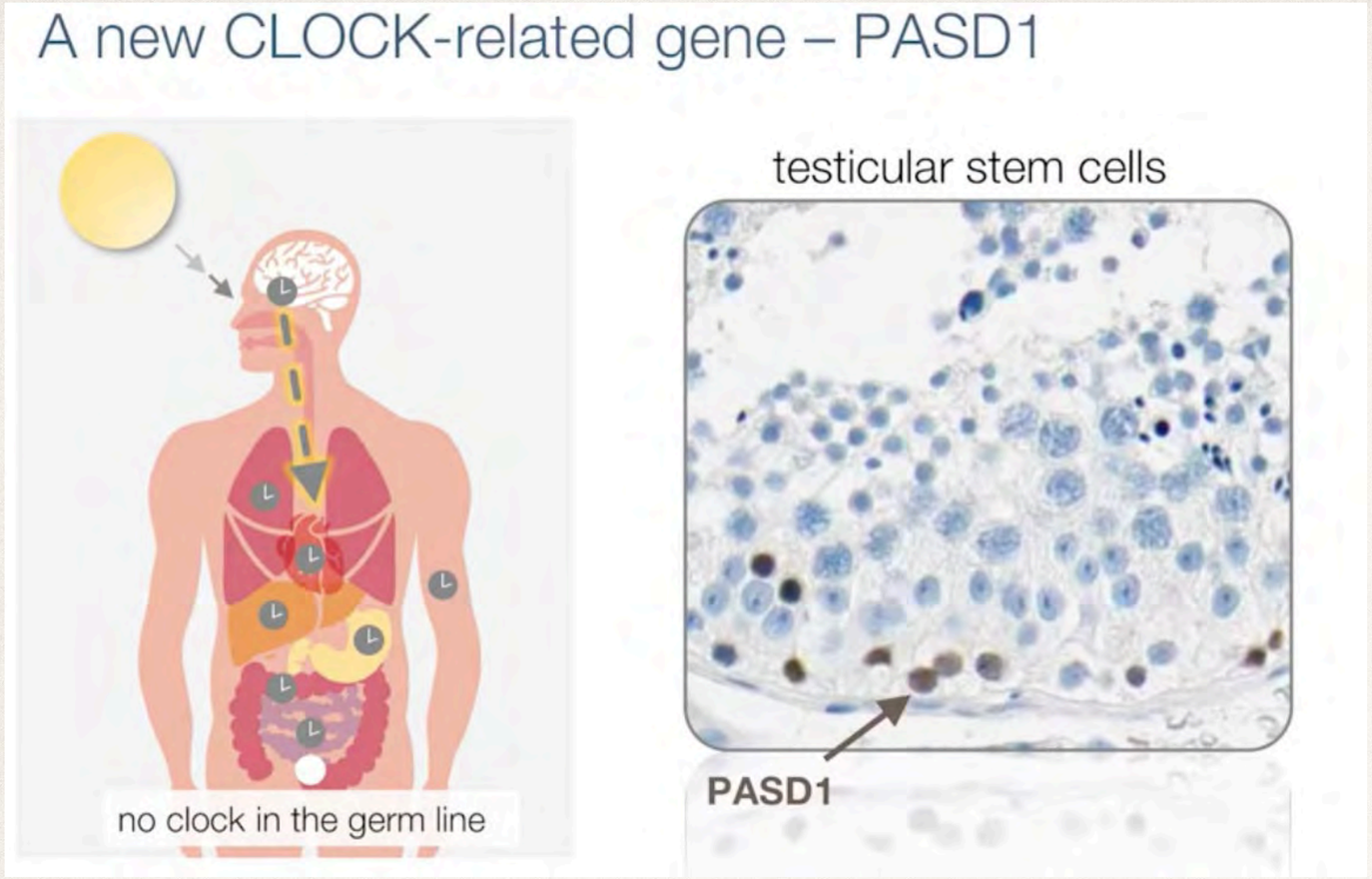


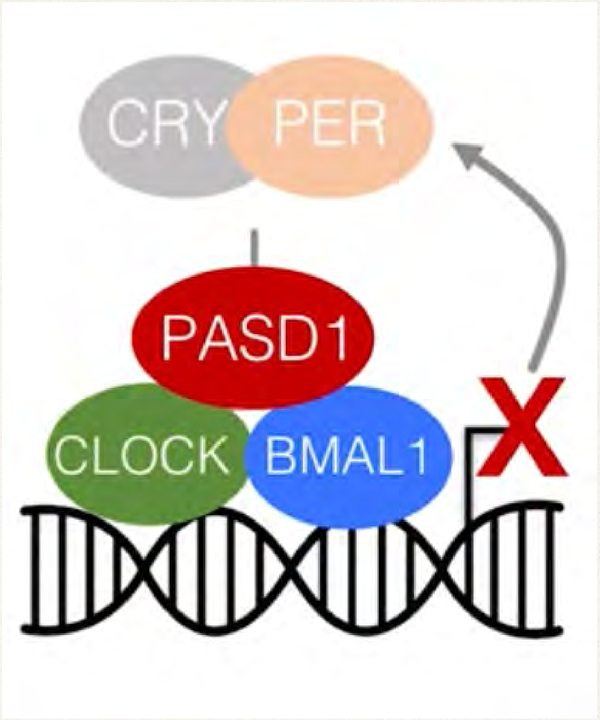
Fritschi et al. Hypotheses for mechanisms linking shiftwork and cancer. *Medical Hypotheses* 2011;77(3):430-436.

Circadian Misalignment and Cancer

According to the World Health Organization Shiftwork is a Carcinogen

"Disruption oof circadian rhythms plays a key role in tumorigenesis and facilitates the establishment of cancer hallmarks" Sulli et al 2019 Interplay between circadian clock and cancer"





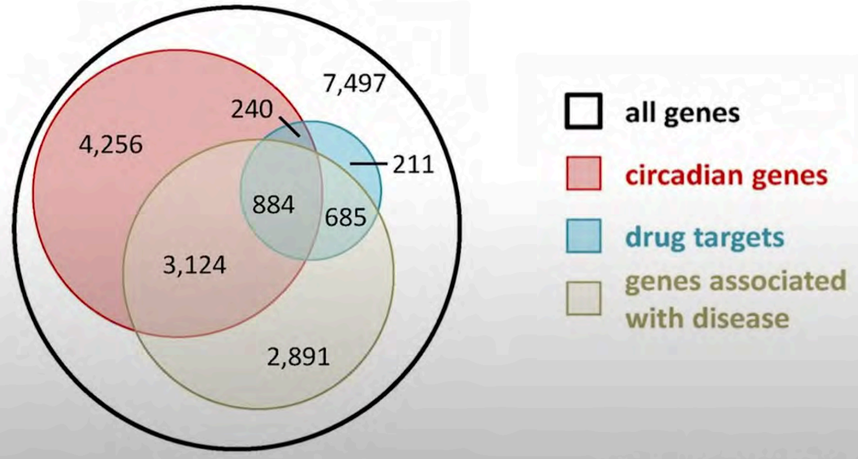
PASD1 (shuts off the clock)

Only in Stem Cells of Testes (only cells in your body that don't have a circadian rhythm)

Never found outside the germline unless cancer is present

Overlap Between Circadian Genes, Known Disease-Associated Genes, and Drug Targets

A 2014 study found rhythmic activity in genes targeted by 56 of the top 100 best-selling drugs in the U.S.



Zhang et al., *PNAS*, Nov. 11, 2014

Effect of immunotherapy time-of-day infusion on overall survival among patients with advanced melanoma in the USA (MEMOIR): a propensity score-matched analysis of a single-centre, longitudinal study

David C Qian, MD • Troy Kleber, MSCR • Brianna Brammer, BS • Karen M Xu, MD • Jeffrey M Switchenko, PhD • James R Janopaul-Naylor, MD • et al. Show all authors

Published: November 12, 2021 • DOI: https://doi.org/10.1016/S1470-2045(21)00546-5 •

Survival Doubles if taken before 430pm

Circadian Pharmacotherapy (aka Chronotherapy)

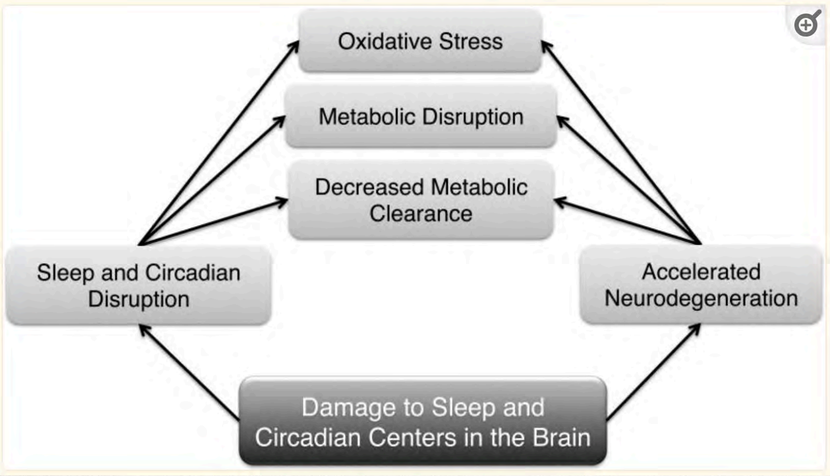
Over 50% of Drugs have a rhythmic target or activity

Which means timing of drug intake is something that needs to be considered with each therapy.

A circadian gene expression atlas in mammals: Implications for biology and medicine

Ray Zhang[a,1], Nicholas F. Lahens[a,1], Heather I. Ballance[a], Michael E. Hughes[b,2], and John B. Hogenesch[a,2]

(Mann–Whitney u test, $P << 10^{-15}$; Fig. 4*C*). Furthermore, oscillating genes were also associated with nearly every major disease funded by National Institutes of Health at significantly higher rates than expected by chance (Fig. S8). Cancer, diabetes mellitus type 2, Alzheimer's disease, schizophrenia, Down's syndrome, obesity, and coronary artery disease were most strongly associated with circadian genes. For example, many of these oscillating genes are involved in neurodegeneration, including *Fus*, *Tdp43*, alpha synuclein, gamma synuclein, *Atxn1*, *Atxn2*, *Atxn3*, *Atxn7*, *Atxn10*, *Psen1*, and *Psen2*. These genes are mutated in



Trends Endocrinol Metab. Author manuscript; available in PMC 2017 Apr 1.
PMCID: PMC4808513
Published in final edited form as:
HHMIMSID: HHMIMS760414
Trends Endocrinol Metab. 2016 Apr; 27(4): 192–203.
PMID: 26947521
Published online 2016 Mar 3. doi: 10.1016/j.tem.2016.02.003

Circadian Rhythms, Sleep, and Disorders o

Joanna Mattis[1] and Amita Sehgal[2]

Do circadian genes contribute to the onset and progression of neurodegeneration? One link is found in Presenilin-2, a protein that is involved in cleaving of amyloid precursor protein and mutations in which are a major cause of autosomal dominant hereditary cases of AD [107]. The *Presenilin-2* gene contains several upstream E-boxes, and is under circadian control, with direct gene activation by both CLOCK and BMAL1 [108]. Evidence from Drosophila suggests another link: SPAGHETTI (SPAG) is a regulator of the circadian kinase DOUBLETIME (DBT) and affects aggregation of Huntingtin [109]. SPAG protects DBT from degradation, stabilizing its expression [110]. Reduction of either DBT or SPAG activates the caspase DRONC, and leads to DRONG-dependent Tau cleavage with increased Tau toxicity and neurodegeneration.

More generally, oxidative stress is hypothesized to be a feature shared across neurodegenerative disorders, and may contribute to protein misfolding and aggregation. Multiple studies link circadian disruption, aging, and oxidative stress. *Drosophila* with a null mutation in the *period* gene showed less resilience to oxidative stress, with increased oxidative damage and increased mortality [111]. These flies also had increased neuronal degeneration relative to age-matched controls, perhaps as a result of impaired stress defense. Double mutant flies containing both the *period* null mutant and a mutation in *sniffer*, which on its own leads to an oxidative stress and neurodegenerative phenotype, displayed accelerated neuronal degeneration and reduced lifespans [112]. In another *Drosophila* study, the breakdown of sleep:wake cycles seen with aging was also seen with increased oxidative stress, suggesting that age-associated accumulation of oxidative damage may contribute to sleep:wake cycle disruption [56].

Several studies have investigated aging and oxidative stress in *Bmal1*$^{-/-}$ mice. These mice have a premature aging phenotype, including accelerated reduction of bone and muscle mass, less subcutaneous fat, decreased hair growth, development of cataracts, and significantly reduced lifespan [113]. Reactive

JCI The Journal of Clinical Investigation
Published by The American Society for Clinical Investigation | Founded 1908

J Clin Invest. 2013 Dec 2; 123(12): 5389–5400.
PMCID: PMC3859381
Published online 2013 Nov 25. doi: 10.1172/JCI70317
PMID: 24270424

Circadian clock proteins regulate neuronal redox homeostasis and neurodegeneration

Erik S. Musiek,[1] Miranda M. Lim,[2] Guangrui Yang,[3] Adam Q. Bauer,[4] Laura Qi,[1] Yool Lee,[3] Jee Hoon Roh,[1] Xilma Ortiz-Gonzalez,[5] Joshua T. Dearborn,[6] Joseph P. Culver,[4] Erik D. Herzog,[7] John B. Hogenesch,[3] David F. Wozniak,[6] Krikor Dikranian,[8] Benoit I. Giasson,[9] David R. Weaver,[10] David M. Holtzman,[1] and Garret A. FitzGerald[3]

Brain aging is associated with diminished circadian clock output and decreased expression of the core clock proteins, which regulate many aspects of cellular biochemistry and metabolism. The genes encoding clock proteins are expressed throughout the brain, though it is unknown whether these proteins modulate brain homeostasis. We observed that deletion of circadian clock transcriptional activators aryl hydrocarbon receptor nuclear translocator–like (*Bmal1*) alone, or circadian locomotor output cycles kaput (*Clock*) in combination with neuronal PAS domain protein 2 (*Npas2*), induced severe age-dependent astrogliosis in the cortex and hippocampus. Mice lacking the clock gene repressors period circadian clock 1 (*Per1*) and period circadian clock 2 (*Per2*) had no observed astrogliosis. *Bmal1* deletion caused the degeneration of synaptic terminals and impaired cortical functional connectivity, as well as neuronal oxidative damage and impaired expression of several redox defense genes. Targeted deletion of *Bmal1* in neurons and glia caused similar neuropathology, despite the retention of intact circadian behavioral and sleep-wake rhythms. Reduction of *Bmal1* expression promoted neuronal death in primary cultures and in mice treated with a chemical inducer of oxidative injury and striatal neurodegeneration. Our findings indicate that BMAL1 in a complex with CLOCK or NPAS2 regulates cerebral redox homeostasis and connects impaired clock gene function to neurodegeneration.

Most metabolic activity is under circadian control, and loss of circadian clocks has been associated with cellular and system-wide deficits in metabolism [121,122]. Sleep loss also has profound effects on metabolism [123–125], which include an increase in markers of insulin resistance. Given these findings, it is tempting to speculate that circadian/sleep disruption confer susceptibility to AD through their regulation of metabolism.

Circadian Genes "strongly associated" with AD

Bace1 and Bace2 (amyloid beta), Presenilin 2 (helps breaks down Amyloid), etc

Multiple studies have shown that β-amyloid levels in the brain have a diurnal variation. A study trending hourly measurements of CSF β-amyloid levels in human subjects revealed significant circadian patterns, with β-amyloid concentrations correlating inversely with the amount of sleep [126]. In a rodent model, interstitial fluid levels of β-amyloid in the brain also fluctuate with the normal sleep-wake cycle [127]. The diurnal variation of β-amyloid levels suggests that β-amyloid may be cleared from the brain during sleep. Consistent with this, sleep deprivation leads to significantly elevated interstitial fluid levels of β-amyloid [128,129] and increased plaque formation [128]. Conversely, enhancing sleep reduces β-amyloid deposition [129].

Poor sleep may age the brain/body thru impaired oxidative stress defense and metabolic disruptions as well

Circadian dysfunction and Alzheimer's disease – An updated review

Faizan Ahmad MSc ✉, Punya Sachdeva BSc, Jasmine Sarkar BSc, Raafiah Izhaar MSc

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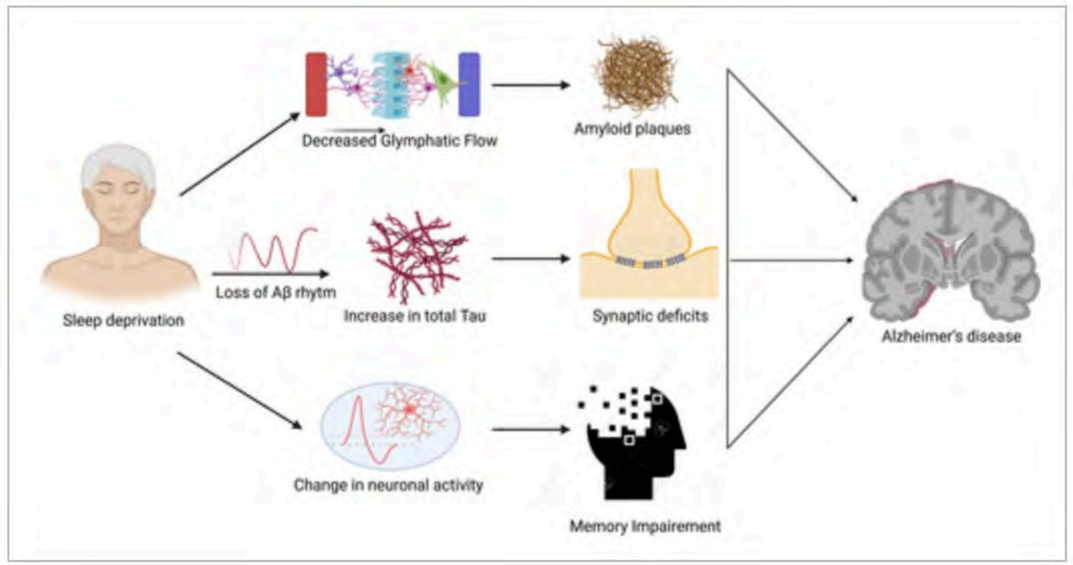
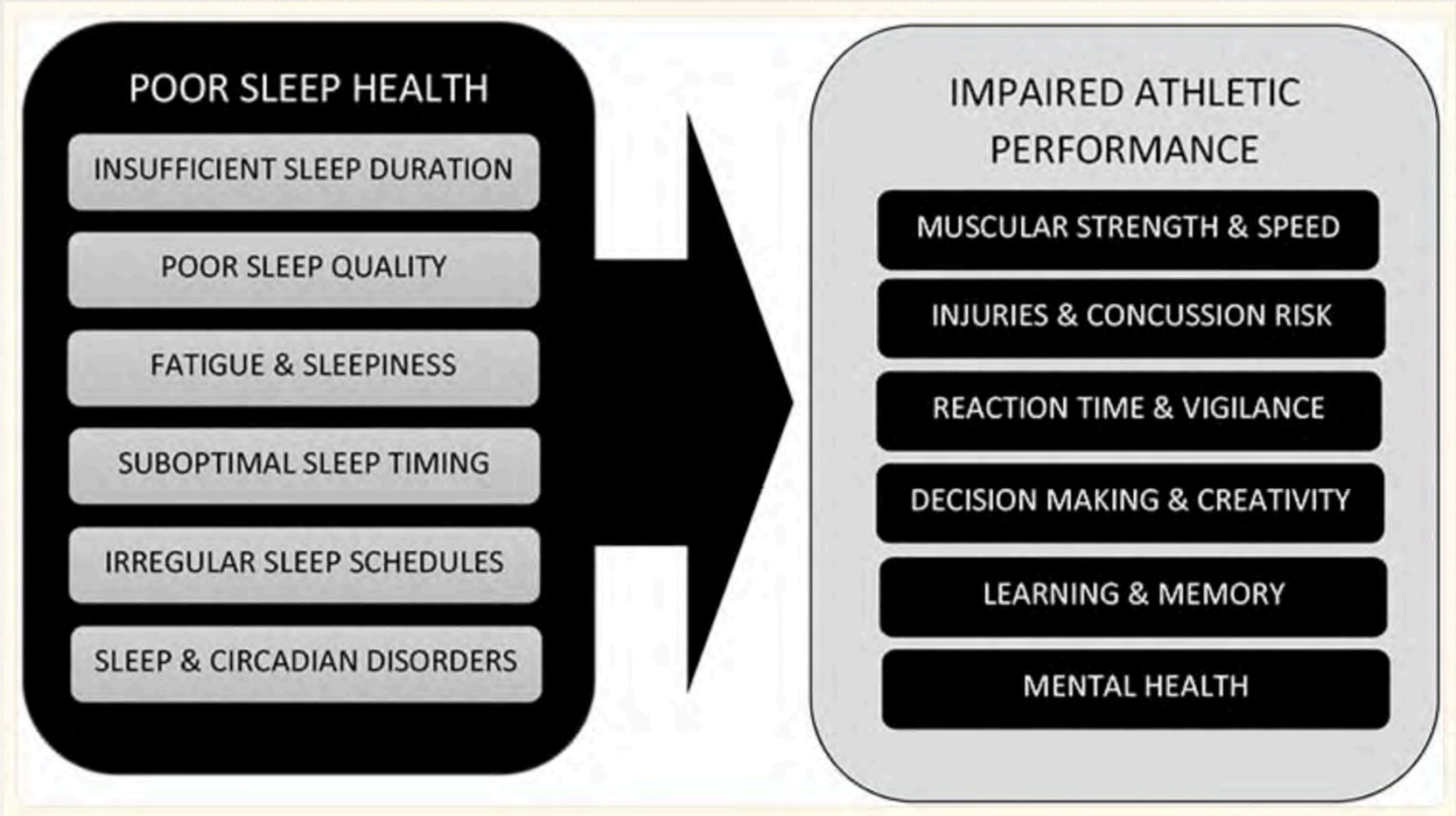


Various animal models show exercise chronobiotic properties. It is difficult to identify whether exercise has chronobiotic properties in humans because it is quite hard to differentiate the range of effects shown by exercise from multiple other factors, like food, social influences, and light.[123] Non-photic stimuli, on the other hand, appear to be capable of synchronizing circadian rhythms in people who are blind who lack sensitivity to light, and this helps them entrain to routine schedules without utilizing exogenous melatonin. A recent study related to circadian rhythms and AD has shown that when a person exercises just before habitual sleep, it accelerates circadian rhythm and if it is performed during habitual sleep time, it delays circadian rhythms.[124-126] Exercise also affects the hippocampus, which plays a role in affecting sleep quality. It has also been reported that people who do exercise regularly on a daily basis have better sleep quality as well as less daytime sleepiness when compared to people who are inactive and do not exercise. As a result, it is still possible that exercise has a greater impact on older adults who face difficulty in sleeping. Exercises also enhance the cognitive part and show neural plasticity which is effective in normal aging as well as a treatment for AD.[127-132] Sleep after exercise has a well-known effect on cognitive performance. According to the recent study findings, physical activity plays a huge role in diminishing the effects of poor sleep quality on cognitive functioning in older adult women. As a result, more research is needed to understand the mechanisms underlying exercise, sleep, and cognitive function that are linked in older adults.[133-138]

Exercise and Neurodegeneration

Could Skeletal BMAL1 work to force deeper sleep which in turn allow better cleaning, repair, and degradation

The article failed to mention the effect of sugar in this matter which like works thru failure to turn on certain important cleaning pathways, produces brain inflammation, and creates insulin resistance in cells of the brain



Circadian Systems in Athletes

FORBIDDEN ZONE

Westward Travelers feel like they are playing at bedtime, Eastward Travelers like they are playing earlier in the day

West Coast Professional Teams (during evening games) beat the point spread twice as often as East Coast Teams

Going to sleep early irrespective of preference or circadian misalignment is associated with better mental and physical health

Be Like Shohei Ohtani

Advice for the Future

Always Join the West Coast Team, Exercise, **Set Wake**, TRE, Phase Advance for PSG/MSLT, Limit Sugar, **Indoor Sunset Transitions**

Avoid Caffeine, Use Standard Time and Informed Circadian Lighting, Limit Shift Work Exposure

Caris Talburt Fitzgerald, MD

fitzgeraldcaris@gmail.com

Individual light history matters to deal with the Antarctic summer

Julieta Castillo [1], André C Tonon [2], María Paz Hidalgo [2], Ana Silva [1 3], Bettina Tassino [4 5]

Affiliations + expand

PMID: 37495664 PMCID: PMC10372057 DOI: 10.1038/s41598-023-39315-y

Weekly, seasonal, and chronotype-dependent variation of dim-light melatonin onset

Giulia Zerbini [1 2 3], Eva C Winnebeck [1], Martha Merrow [1]

Affiliations + expand

PMID: 33608951 DOI: 10.1111/jpi.12723

Reentrainment of the circadian pacemaker during jet lag: East-west asymmetry and the effects of north-south travel

Casey O Diekman [1], Amitabha Bose [2]

Affiliations + expand

PMID: 28987464 DOI: 10.1016/j.jtbi.2017.10.002

Length of Daylight

Adaptation to Travel North/South Relies on Sleep History and Habits

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We function best in certain latitudes which are also the best temperature matches for us, but thanks to the design of the rhythm can function anywhere

Would the data be more robust if other circadian variables were considered?

Table 3. Changes in Cardiovascular Risk Factors during 12-Month Trial Period.*

Variable	Time-Restricted Eating (N=69)	Daily Calorie Restriction (N=70)	Difference between Groups (95% CI)
	Change from baseline (95% CI)		
Systolic blood pressure — mm Hg			
6 mo	−10.1 (−12.4 to −7.8)	−8.1 (−10.3 to −5.9)	−1.9 (−5.1 to 1.2)
12 mo	−8.1 (−10.4 to −5.7)	−7.7 (−10.1 to −5.4)	−0.3 (−3.7 to 3.1)
Diastolic blood pressure — mm Hg			
6 mo	−6.0 (−7.8 to −4.2)	−5.1 (−6.8 to −3.3)	−0.9 (−3.4 to 1.6)
12 mo	−5.1 (−7.1 to −3.1)	−3.8 (−5.7 to −2.0)	−1.3 (−4.1 to 1.6)
Pulse — beats/min			
6 mo	−3.1 (−5.4 to −0.9)	−2.4 (−4.5 to −0.2)	−0.8 (−3.9 to 2.4)
12 mo	−1.6 (−4.0 to 0.8)	−1.9 (−4.1 to 0.3)	0.3 (−2.9 to 3.5)
Triglycerides — mg/dl			
6 mo	−44.8 (−60.0 to −29.5)	−31.7 (−46.6 to −16.8)	−13.1 (−34.6 to 8.4)
12 mo	−25.5 (−42.2 to −8.8)	−19.6 (−35.9 to −3.4)	−5.9 (−28.5 to 16.8)
Total cholesterol — mg/dl			
6 mo	−9.0 (−15.9 to −2.2)	−13.7 (−20.2 to −7.2)	4.7 (−4.8 to 14.1)
12 mo	−7.3 (−14.3 to −0.3)	−9.3 (−15.9 to −2.6)	1.9 (−7.9 to 11.7)
High-density lipoprotein cholesterol — mg/dl			
6 mo	4.2 (2.4 to 6.1)	2.7 (0.9 to 4.4)	1.6 (−1.0 to 4.1)
12 mo	4.6 (2.6 to 6.5)	2.9 (1.1 to 4.8)	1.6 (−1.1 to 4.3)
Low-density lipoprotein cholesterol — mg/dl			
6 mo	−5.9 (−12.0 to 0.1)	−11.3 (−17.1 to −5.6)	5.4 (−2.9 to 13.7)
12 mo	−8.4 (−14.7 to −2.1)	−8.9 (−15.1 to −2.8)	0.5 (−8.5 to 9.5)
Glucose level — mg/dl			
6 mo	−5.0 (−8.5 to −1.6)	−4.1 (−7.4 to −0.7)	−1.0 (−5.8 to 3.8)
12 mo	−3.5 (−7.6 to 0.5)	−3.0 (−6.7 to 0.7)	−0.6 (−6.1 to 4.9)
2-hour postprandial glucose — mg/dl			
6 mo	−15.4 (−23.7 to −7.1)	−10.6 (−18.6 to −2.6)	−4.8 (−16.3 to 6.6)
12 mo	−10.8 (−19.7 to −2.0)	−12.1 (−20.2 to −3.9)	1.3 (−10.8 to 13.3)
HOMA–IR index value			
6 mo	−1.4 (−1.9 to −0.8)	−1.2 (−1.8 to −0.6)	−0.2 (−1.0 to 0.6)
12 mo	−1.0 (−1.7 to −0.4)	−0.5 (−1.1 to 0.1)	−0.5 (−1.4 to 0.4)
Insulin disposition index†			
6 mo	−4.6 (−11.4 to 2.2)	−3.3 (−10.0 to 3.5)	−1.3 (−10.9 to 8.2)
12 mo	−6.7 (−18.5 to 5.1)	0.6 (−8.6 to 9.8)	−7.3 (−20.8 to 6.2)

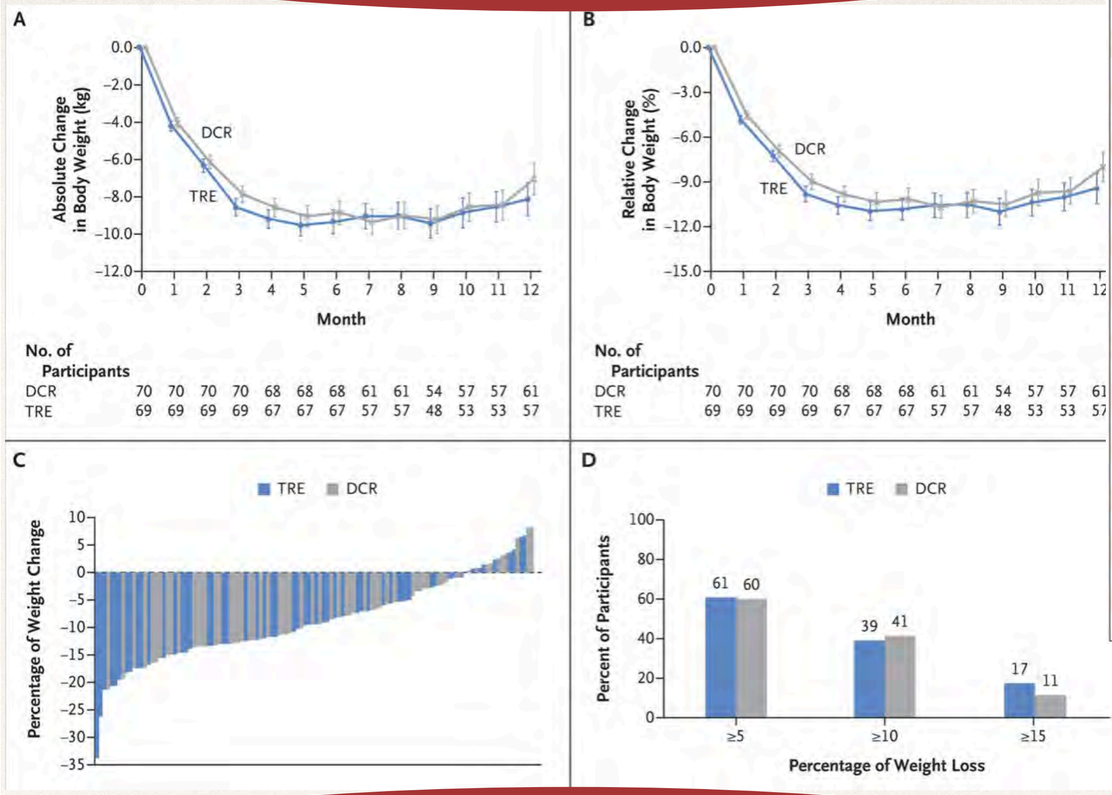


Table 2. Effects of Diets on Weight Loss and Body Composition.*

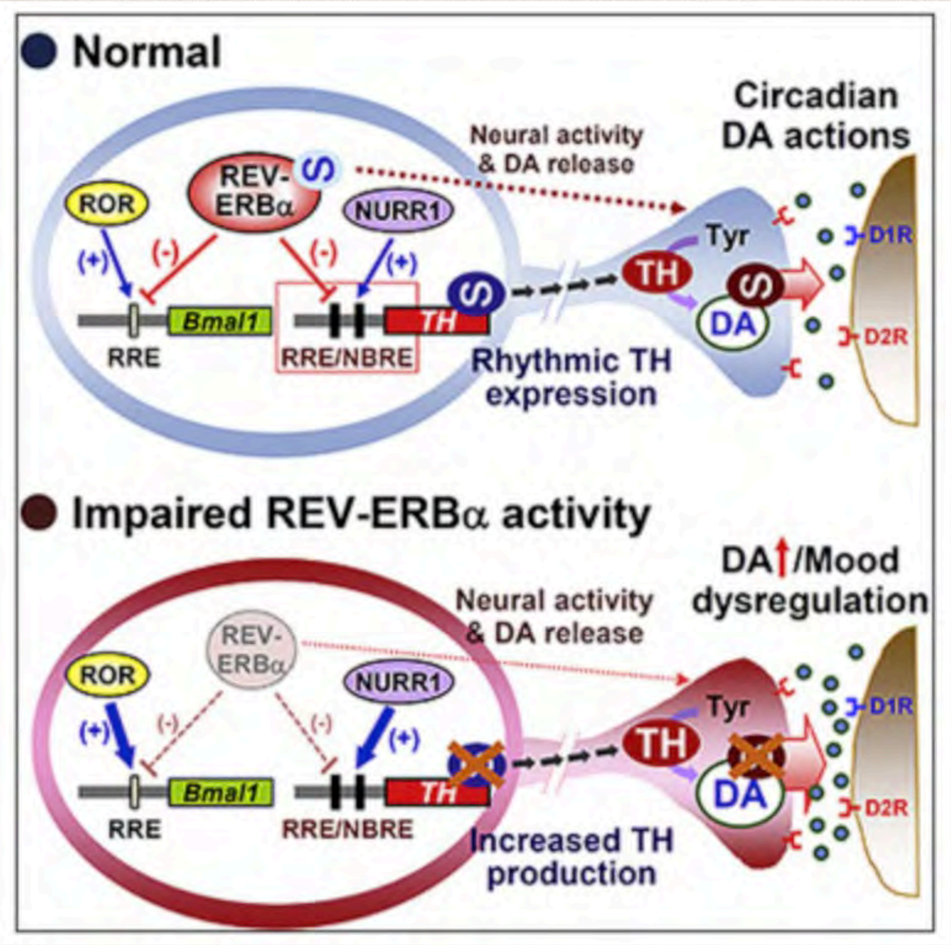
Variable	Time-Restricted Eating (N=69)	Daily Calorie Restriction (N=70)	Difference between Groups (95% CI)
	Change from baseline (95% CI)		
Body weight — kg			
6 mo	−9.4 (−10.8 to −7.9)	−8.9 (−10.3 to −7.4)	−0.5 (−2.6 to 1.6)
12 mo	−8.0 (−9.6 to −6.4)	−6.3 (−7.8 to −4.7)	−1.8 (−4.0 to 0.4)
Body-mass index			
6 mo	−3.4 (−3.9 to −2.9)	−3.2 (−3.7 to −2.7)	−0.2 (−1.0 to 0.5)
12 mo	−2.9 (−3.5 to −2.3)	−2.3 (−2.8 to −1.7)	−0.7 (−1.5 to 0.1)
Waist circumference — cm			
6 mo	−9.4 (−11.0 to −7.9)	−8.7 (−10.2 to −7.3)	−0.7 (−2.8 to 1.4)
12 mo	−8.8 (−10.4 to −7.1)	−7.0 (−8.5 to −5.4)	−1.8 (−4.0 to 0.5)
Body fat mass — kg			
6 mo	−6.9 (−8.0 to −5.7)	−6.4 (−7.5 to −5.3)	−0.5 (−2.0 to 1.1)
12 mo	−5.9 (−7.1 to −4.7)	−4.5 (−5.6 to −3.3)	−1.5 (−3.1 to 0.2)
Body lean mass — kg			
6 mo	−1.9 (−2.4 to −1.4)	−1.7 (−2.2 to −1.2)	−0.2 (−0.9 to 0.5)
12 mo	−1.7 (−2.3 to −1.1)	−1.4 (−2.0 to −0.9)	−0.3 (−1.1 to 0.5)
Body fat percent — %			
6 mo	−4.7 (−5.6 to −3.8)	−4.4 (−5.3 to −3.5)	−0.3 (−1.6 to 1.0)
12 mo	−4.3 (−5.3 to −3.3)	−3.0 (−3.9 to −2.0)	−1.3 (−2.7 to 0.1)
Area of abdominal visceral fat — cm^2			
6 mo	−32.9 (−41.1 to −24.8)	−31.3 (−39.2 to −23.4)	−1.7 (−13.0 to 9.7)
12 mo	−26.0 (−35.0 to −17.1)	−21.1 (−29.5 to −12.8)	−4.9 (−17.3 to 7.5)
Area of abdominal subcutaneous fat — cm^2			
6 mo	−70.1 (−85.2 to −55.1)	−49.2 (−64.1 to −34.4)	−20.9 (−42.0 to 0.2)
12 mo	−53.2 (−71.9 to −34.6)	−37.0 (−52.1 to −21.9)	−16.2 (−39.2 to 6.8)

Noncaloric Beverages Permitted Anytime

New England Journal TRE vs CR

First Study ended at 8pm with unlimited Coke Zero outside of eating times. Second ended at 4pm also with unlimited Coke Zero

Technically TRE out performed CR on every overall measurement but that was reported as nonsignificant (4lbs difference after 12 months without light, sleep, and beverage interventions)



Impact of Circadian Nuclear Receptor REV-ERBα on Midbrain Dopamine Production and Mood Regulation

Sooyoung Chung [1], Eun Jeong Lee [1], Seongsik Yun [1], Han Kyoung Choe [1], Seong-Beom Park [2], Hyo Jin Son [3], Kwang-Soo Kim [4], Dean E. Dluzen [5], Inah Lee [2], Onyou Hwang [3], Gi Hoon Son [6], Kyungjin Kim [1 2]

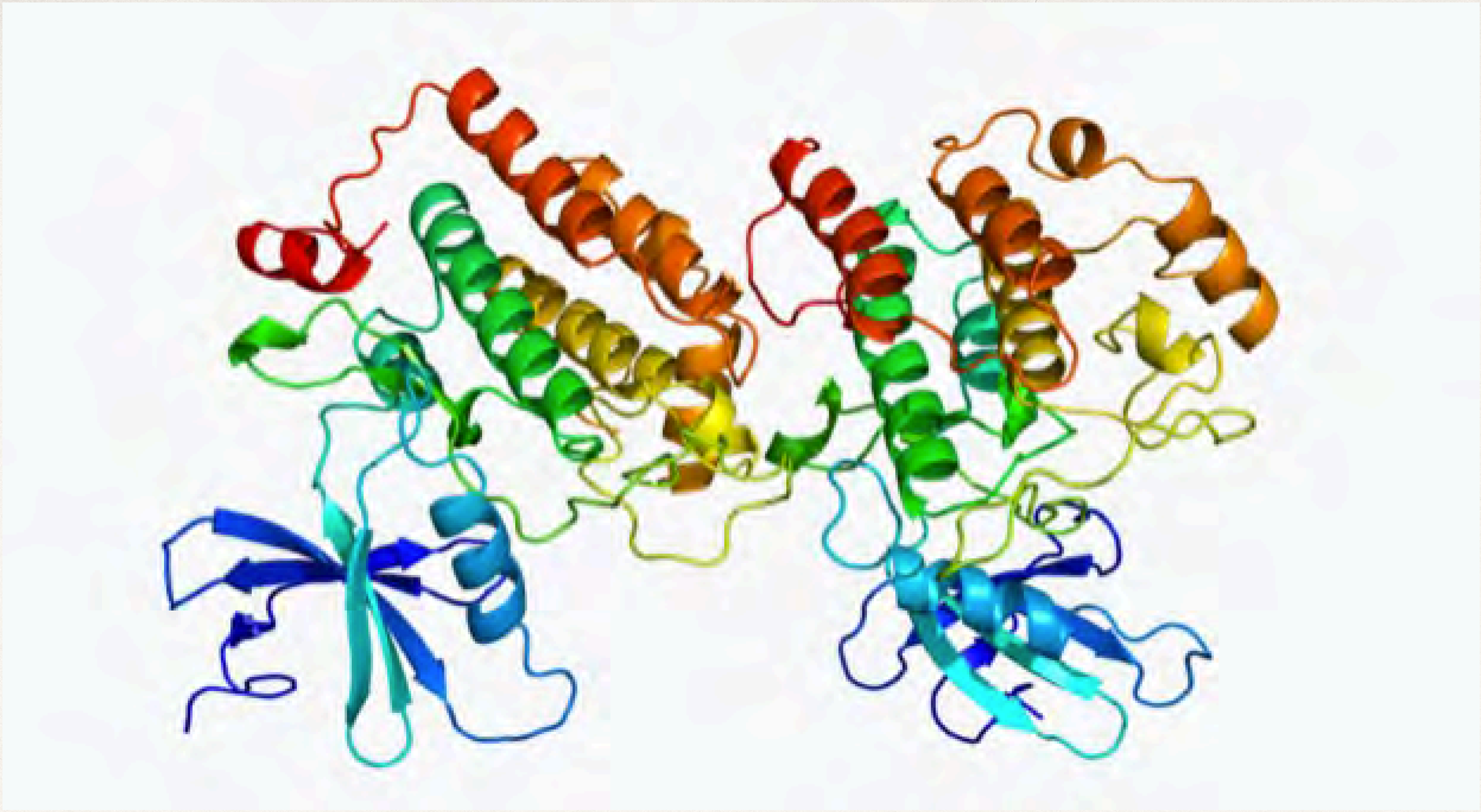
Highlights

- Altered midbrain REV-ERBα induces mania-like behavior and a hyperdopaminergic state
- Tyrosine hydroxylase (*TH*) gene transcription is directly repressed by REV-ERBα
- REV-ERBα and NURR1 antagonistically regulate cyclic *TH* gene transcription
- REV-ERBα controls circadian histone modification of the *TH* promoter

REV-ERBs(represses) and RORs(activates)

Controls expression of CLOCK and BMAL1 (majority of drug targets target REV-ERB/ROR and CK1and2)

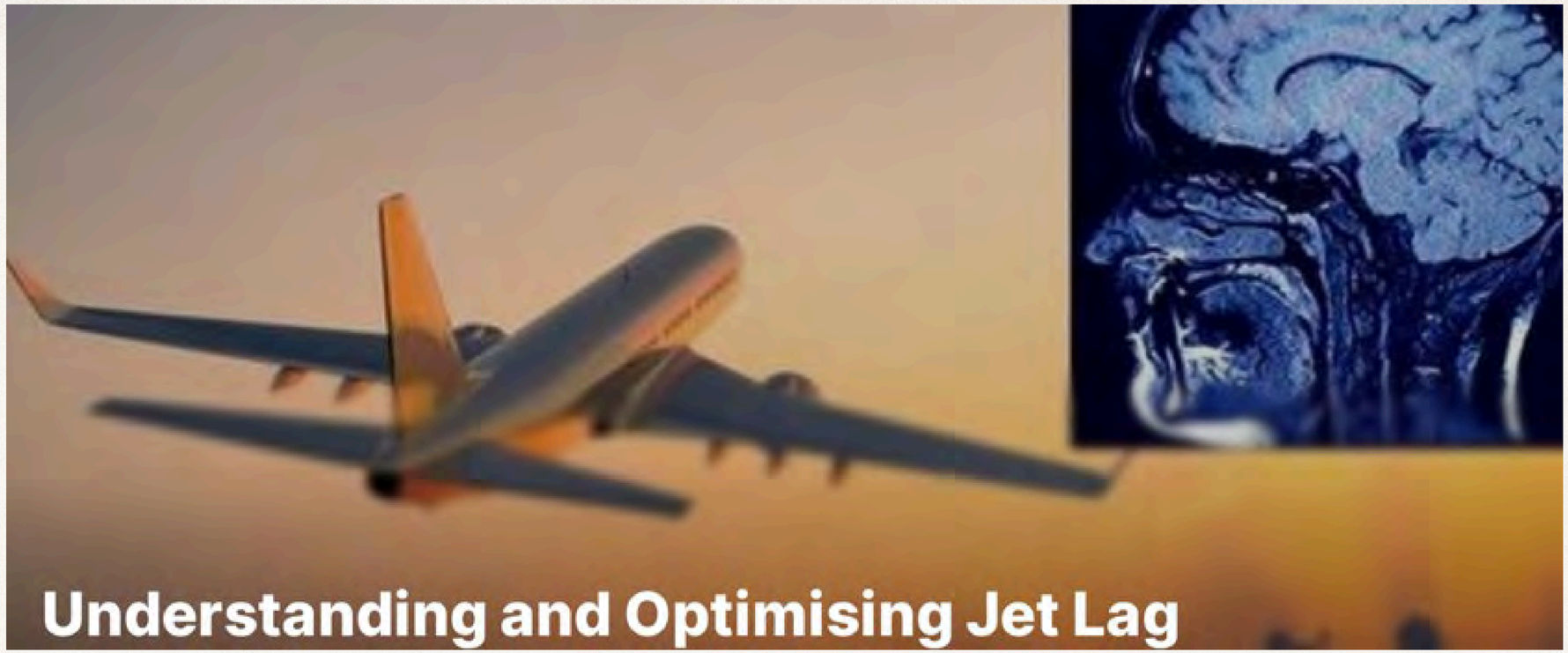
Potential Drug Targets to Boost Circadian Transcription. Nobiletin(potent clock amplitude enhancer with beneficial effects on metabolism and increased longevity in mice) is a ROR agonist (it is a natural compound found in citrus peels)



Casin Kinases (CK1 and CK2 interact with PER)

Diverse Activities (Circadian Rhythms, DNA Repair, Apoptosis, Cell Differentiation)

CK1 inhibitor (Phase Delay Effect), CK2 inhibitor (Lengthens Circadian Period, inhibit growth of Human RCC, and Mouse Leukemia Cells)



Jet Lag Resistance

Teneurin 3 (Tenm3)

Adhesion Molecule highly expressed in Vasoactive Intestinal Peptide (VIP) neurons located in the core region of the SCN

Deficient mice have a higher sensitivity to light and faster re-entrainment to phase advances (possibly due to increased associations between VIP and AVP neurons

EASTWARD TRAVEL

PRETRAVEL
Avoid Sleep Deprivation, Get Enough Sleep
2-3days prior shift bed and meal time early by 1-2hrs

DURING TRAVEL
Stay Hydrated
Avoid Alcohol and Caffeine
Maximize Rest/Sleep
20-30min Naps at Circadian Nadir
Exposure to Light at Mid AM (30-60min)
Avoid Light Mid Afternoon
Exercise in the Late Afternoon
Sleep on the Plane
Stay Awake until an Early Local Bedtime

WESTWARD TRAVEL

PRETRAVEL
Avoid Sleep Deprivation, Get Enough Sleep
2-3days prior shift bed and meal time later by 1-2hrs

DURING TRAVEL
Stay Hydrated
Avoid Alcohol and Caffeine
Maximize Rest/Sleep
20-30min Naps at Circadian Nadir
Exposure to Light Late Afternoon (30-60min)
Avoid Light late PM
Exercise in the Early Morning
Stay Awake on the Plane
Stay Awake until an Early Local Bedtime

30% turn off electronics before bed
29% read
25% have sex
22% drink tea or other nonalcoholic beverage
21% meditate or do breathing exercises
20% stretch
20% smoke a cigarette or vape
19% smoke marijuana
15% drink an alcoholic beverage

47% use a fan
29% use blackout curtains
33% experience disrupted sleep
20% use noise machines
18% use apps
16% use ear plugs
39% take a bath or shower
34% consistent bedtime

2023 AASM Survey of 2000 Adults

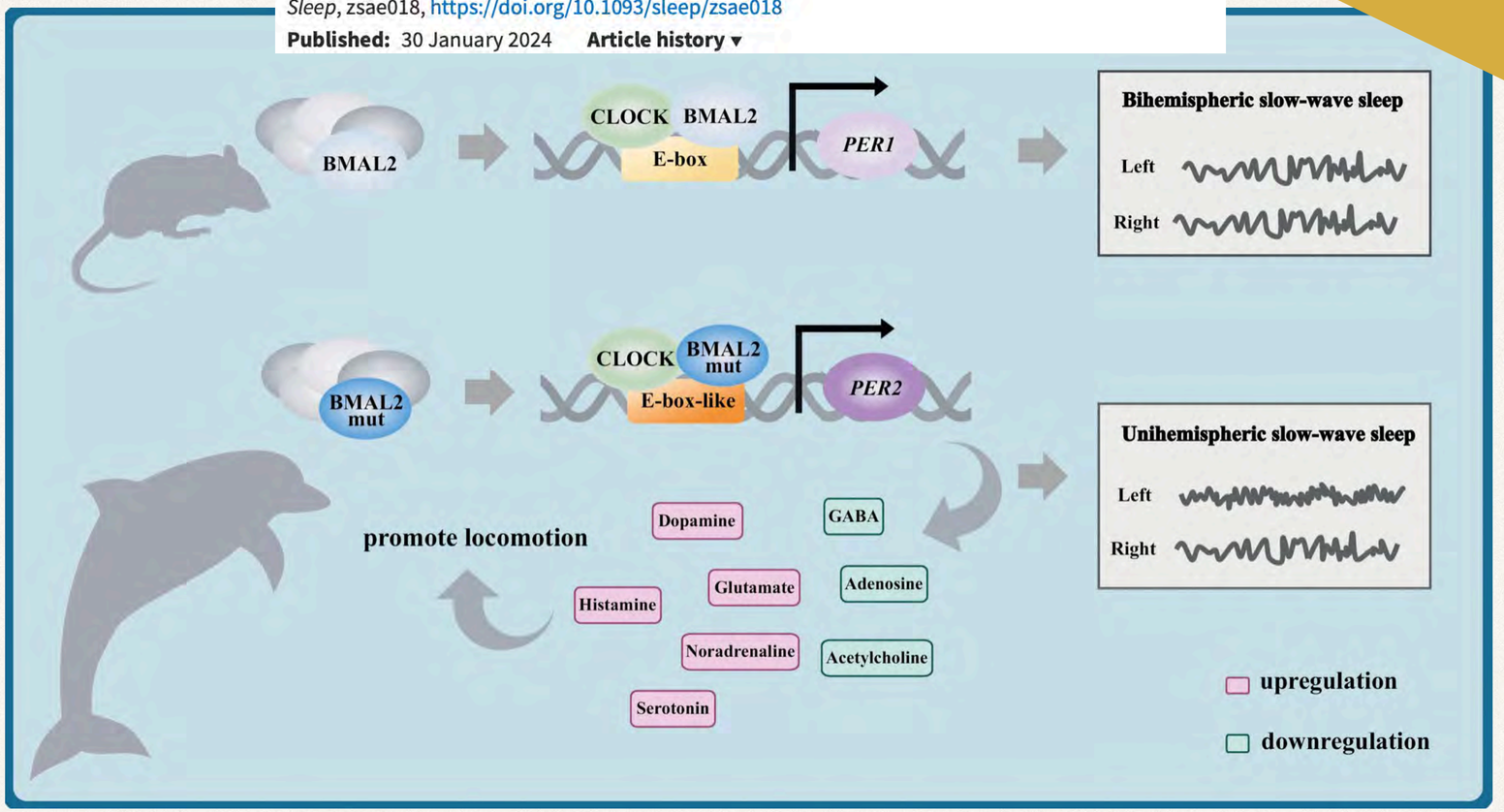
Interesting Sleep Facts

Adaptive changes in *BMAL2* with increased locomotion associated with the evolution of unihemispheric slow-wave sleep in mammals

Daiqing Yin, Biao Zhang, Yujie Chong, Wenhua Ren, Shixia Xu ✉, Guang Yang ✉ Author Notes

Sleep, zsae018, https://doi.org/10.1093/sleep/zsae018
Published: 30 January 2024 **Article history ▾**

Would be interesting to see the genetics of this gene in GBWR sleep deprivation holders



BMAL2 mutation and Hemispheric Sleep

Adaptive Changes in BMAL2 may allow up regulation of arousal genes and downregulation of sleep promoting genes

Needed to maintain hemispheric Sleep