بسم الله الرحمن الرحیم

هُوَ الَّذی جَعَلَ لَکُمُ اللَّیْلَ لِتَسْکُنُوا فیهِ وَ النَّهارَ مُبْصِراً إِنَّ فی ذلِکَ لَآیاتٍ لِقَوْمٍ یَسْمَعُونَ

یونس (۶۷)

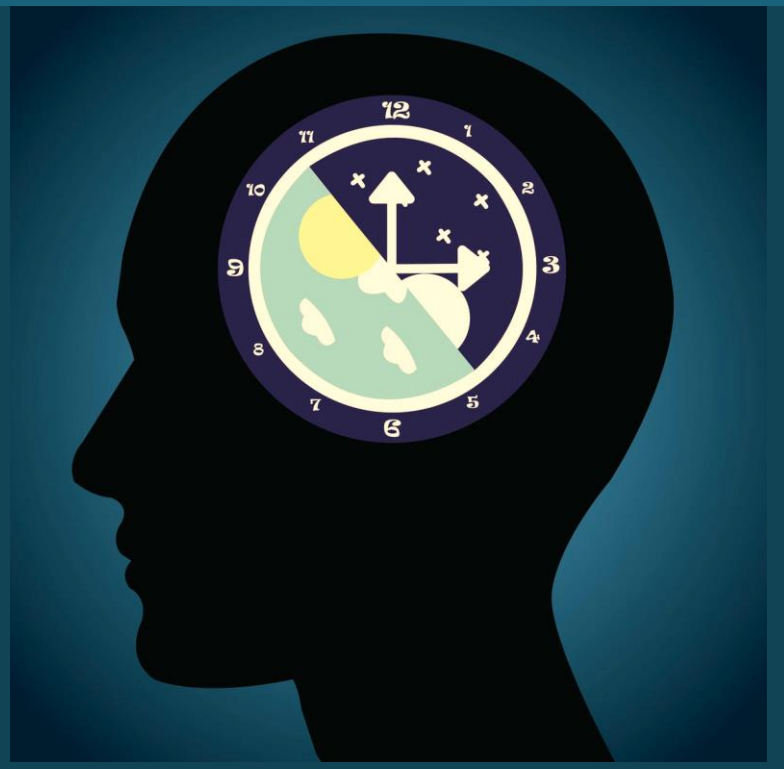
اوست کسی که شب [تاریک] را برای شما پدید آورد تا در آن بیارامید، و روز را نور افشان [قرار داد تا در آن به کار و کوشش بپردازید]؛ یقیناً در این امور برای گروهی که حقایق را بشنوند، نشانه هایی [از توحید و قدرت و ربوبیّت خدا] ست.

وجَعَلْنا نَوْمَکُمْ سُباتاً

(۹) النبا

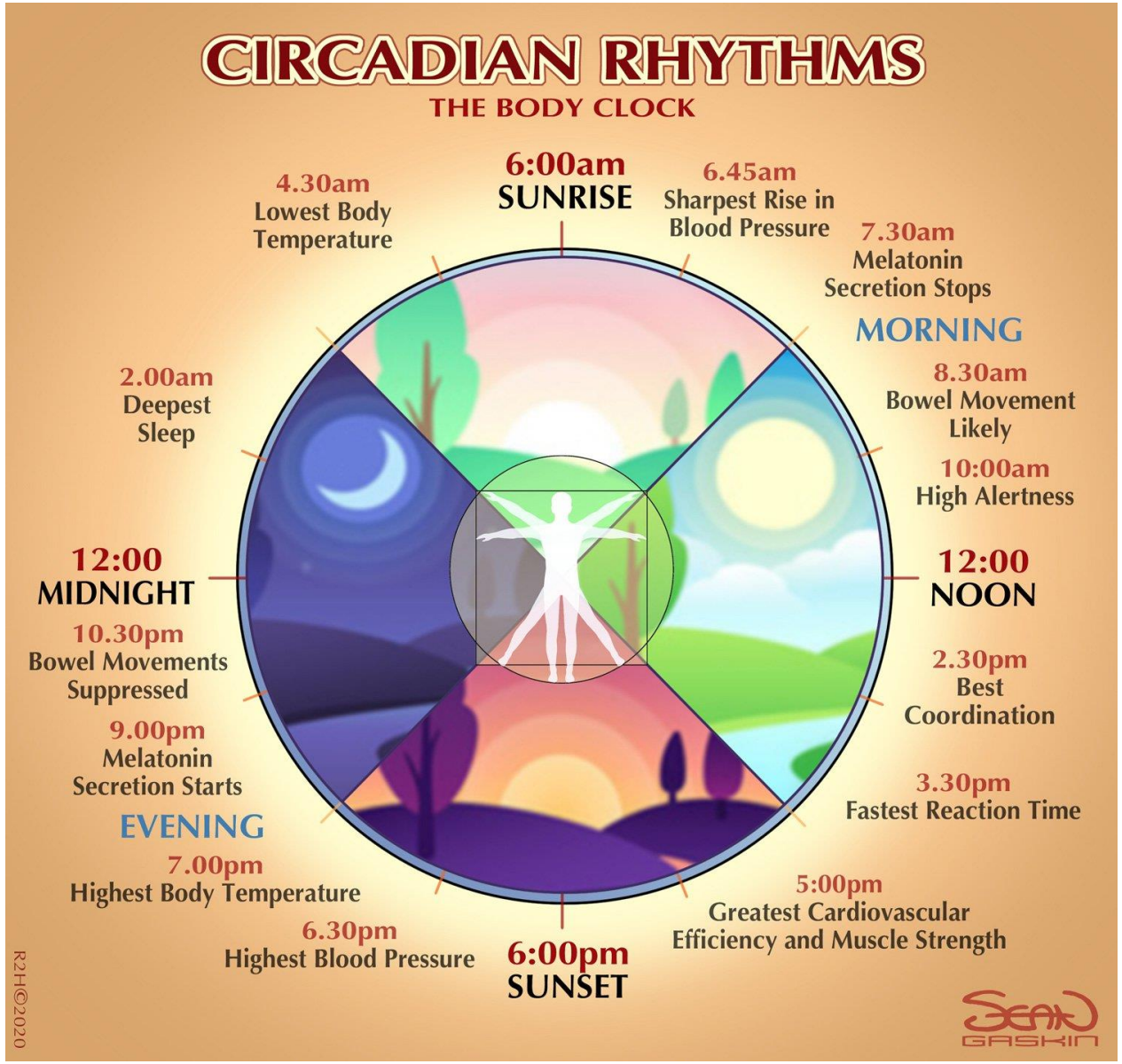
و خوابتان را مایه استراحت و آرامش [و تمدّد اعصاب] قرار دادیم

Circadian Rhythms



Introduction

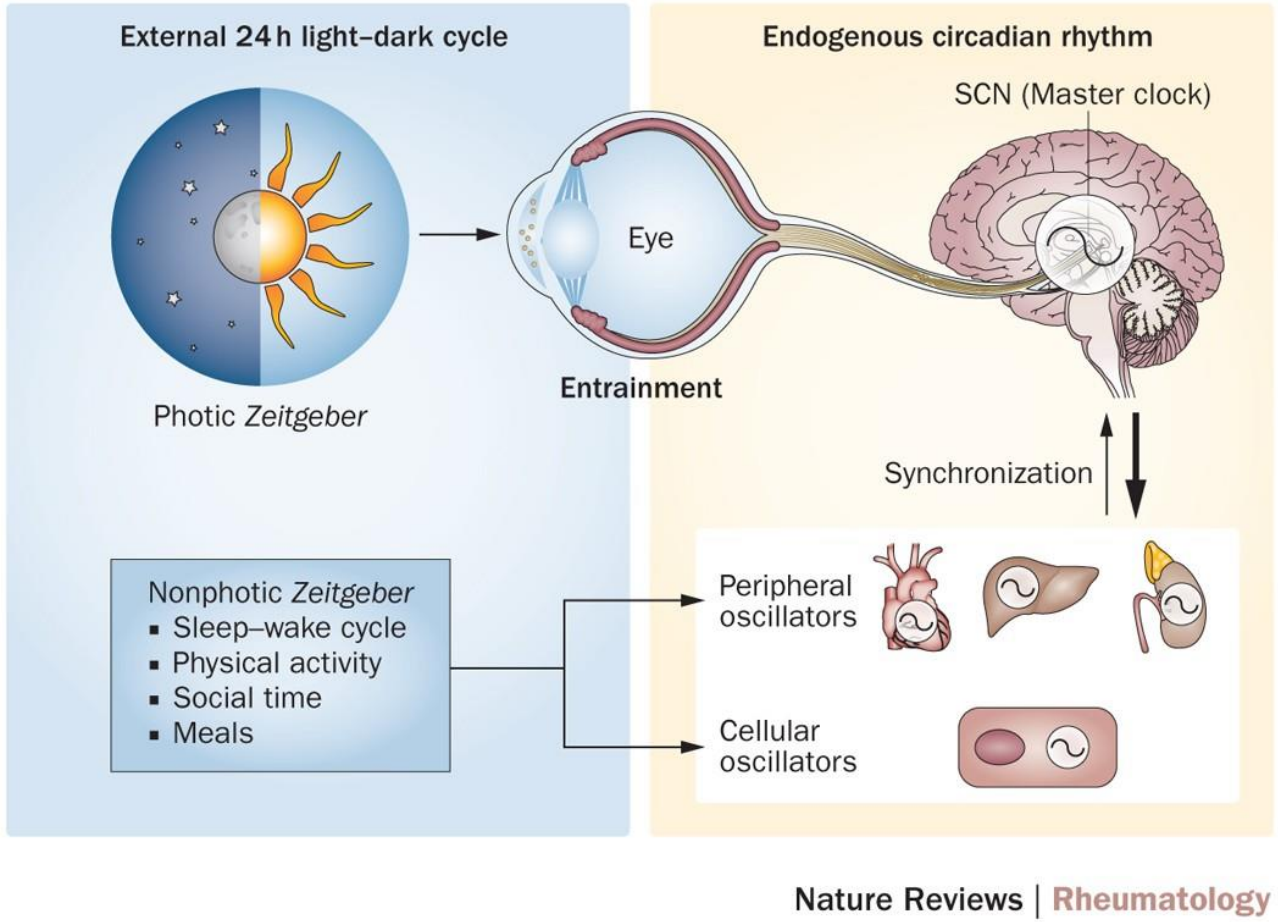
- Almost all life on earth uses an internal biological clock to anticipate the profound changes that result from the Earth' s rotation upon its axis.
- The Nobel Prize in Physiology or Medicine 2017 was awarded jointly to Jeffrey C. Hall, Michael Rosbash and Michael W. Young for their work on the molecular mechanisms controlling the circadian rhythms.
- A **circadian rhythm** or **circadian cycle**, is a natural, internal process that regulates the sleep–wake cycle and repeats roughly every 24 hours. It can refer to any process that originates within an organism (i.e., endogenous) and responds to the environment (entrained by the environment).
- The term *circadian* comes from the ***circa***, meaning "around" (or "approximately"), and ***diēm***, meaning "day".
- Chronobiology is a field that studies the effects of time on biological systems. Periodicity is of particular interest.



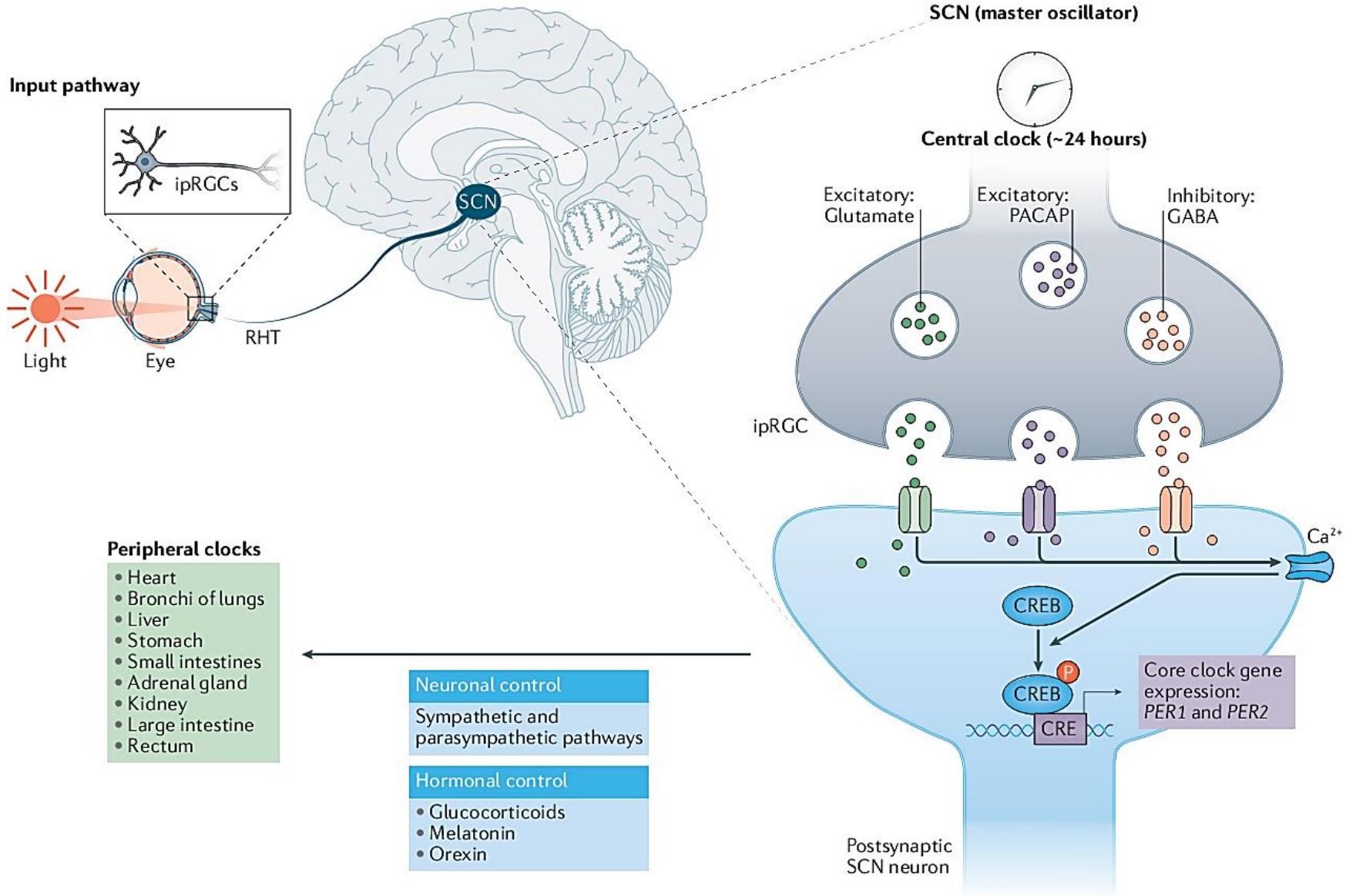
Internal circadian clocks and external Zeitgebers

Exogenous rhythms are **Zeitgebers** that means **environmental time cues** such as sunlight, alarm clocks, or social interaction that helps trigger an organism to entrainment to a 24-hour cycle.

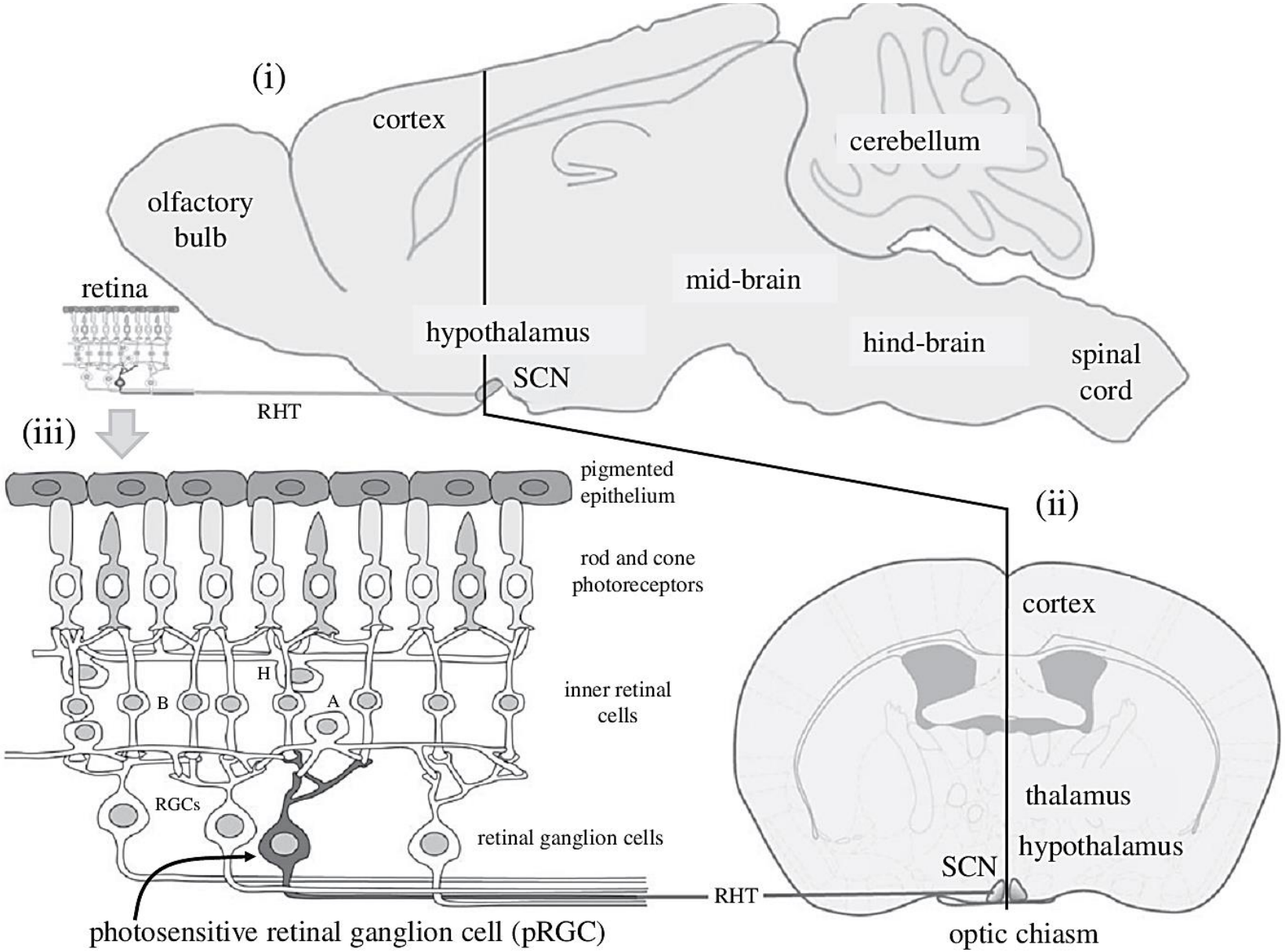
Endogenous biological rhythms are **naturally occurring cycles within our bodies**. Endogenous means that it is 'built in' and it naturally occurs within our body.



Hierarchical organization of the mammalian clock system

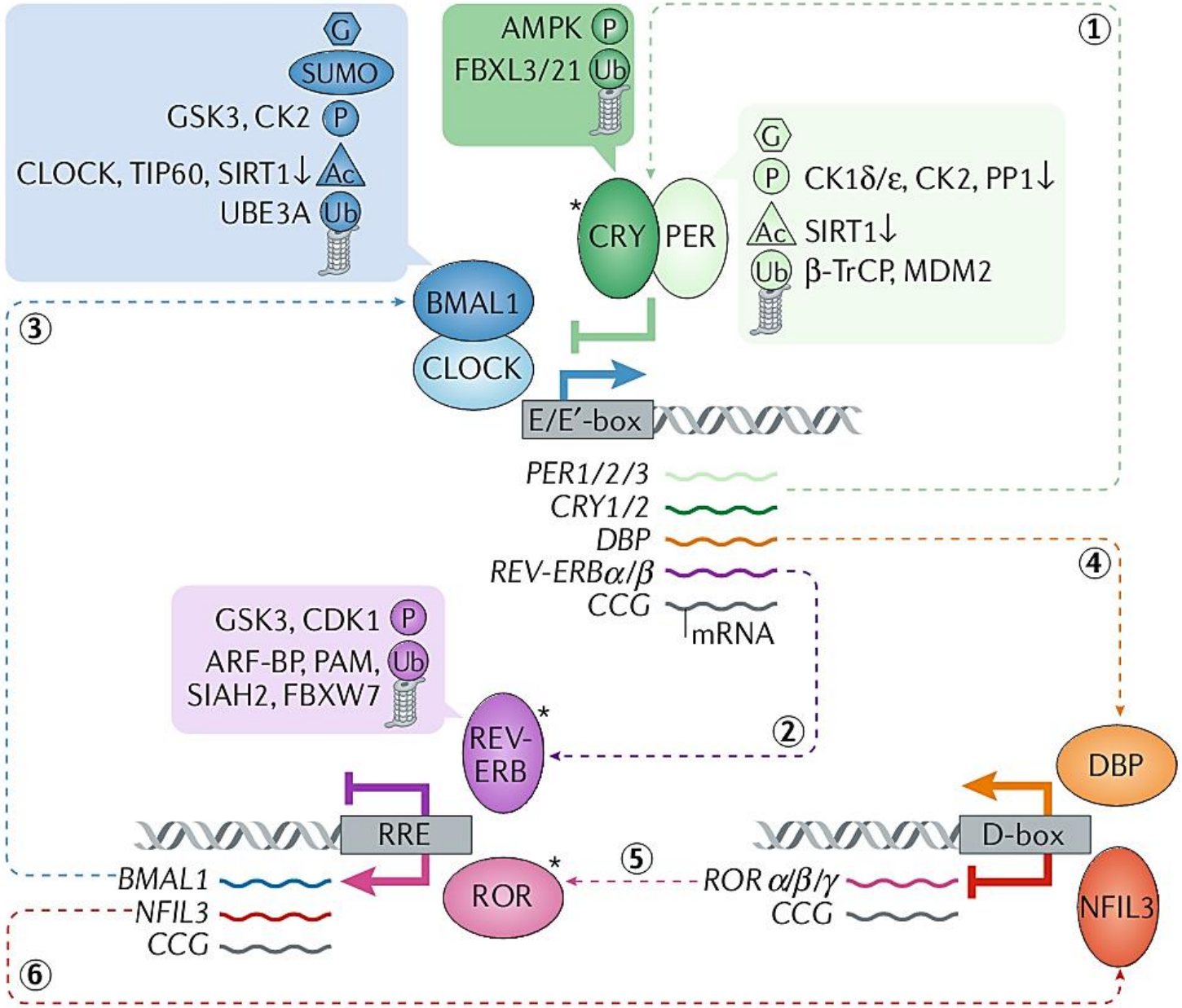


Central clock

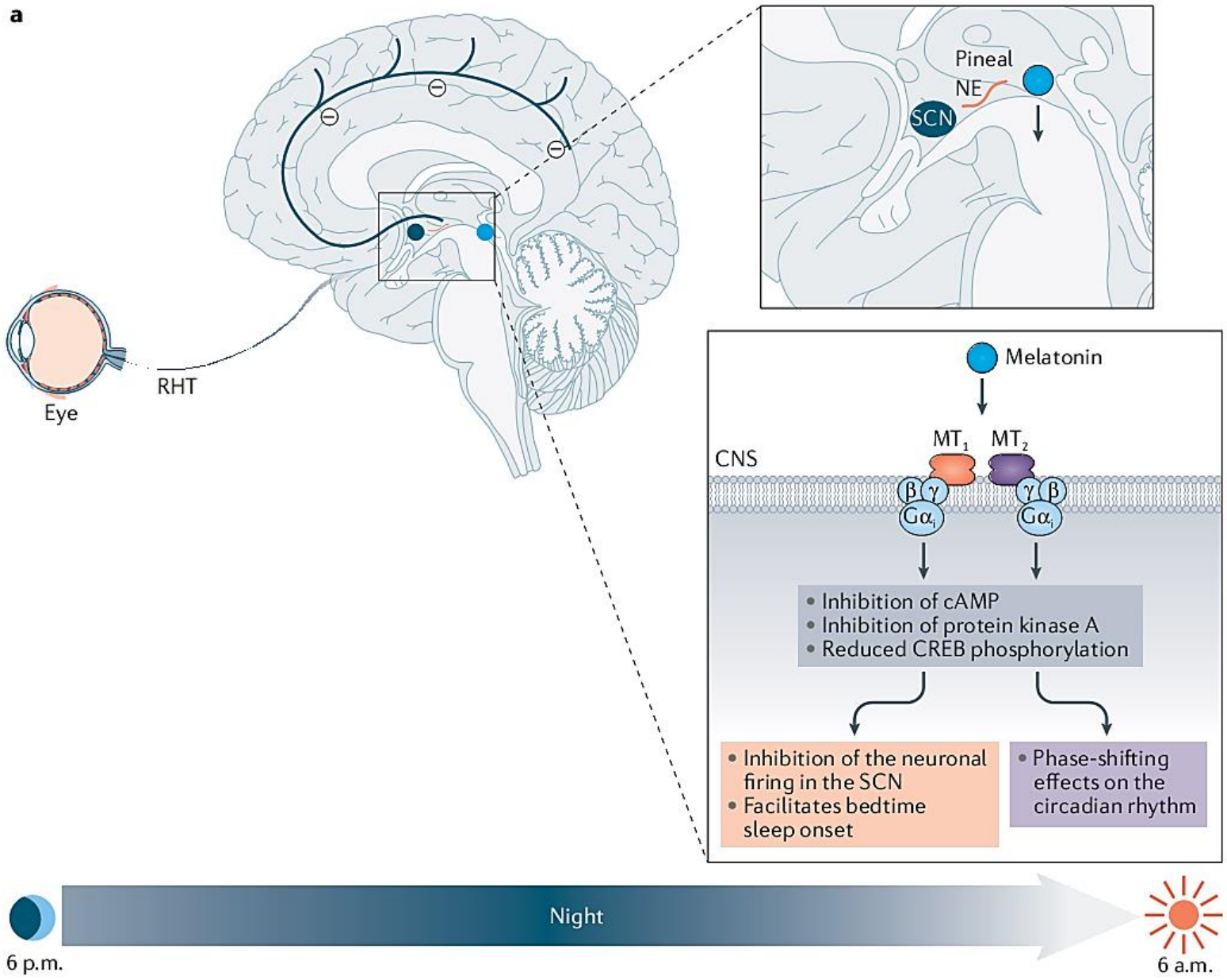


The transcription–translation feedback loop

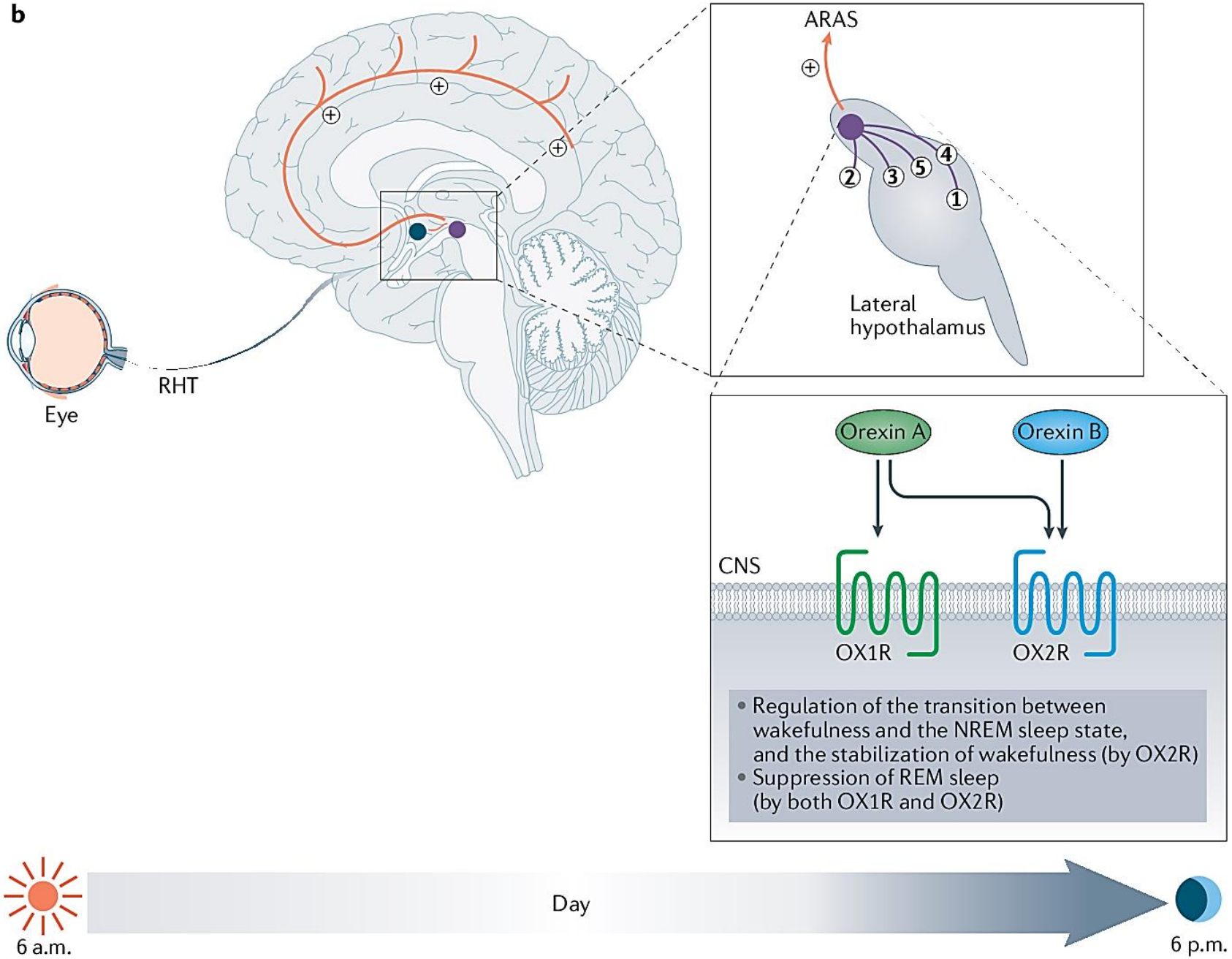
- The circadian transcriptional machinery consists of two transcription factors, CLOCK and BMAL1 (the activators) that heterodimerize and bind to the E-Box sequences of the promoters of ~10-15% of our genes to direct their rhythmic transcription.
- This transcriptional activity peaks during the day but is inhibited at night by the proteins period (PER) and cryptochrome (CRY) (the repressors).
- Additionally, several kinases and phosphatases regulate the phosphorylation of both activators and repressors, controlling the localization and stability of these integral clock proteins.



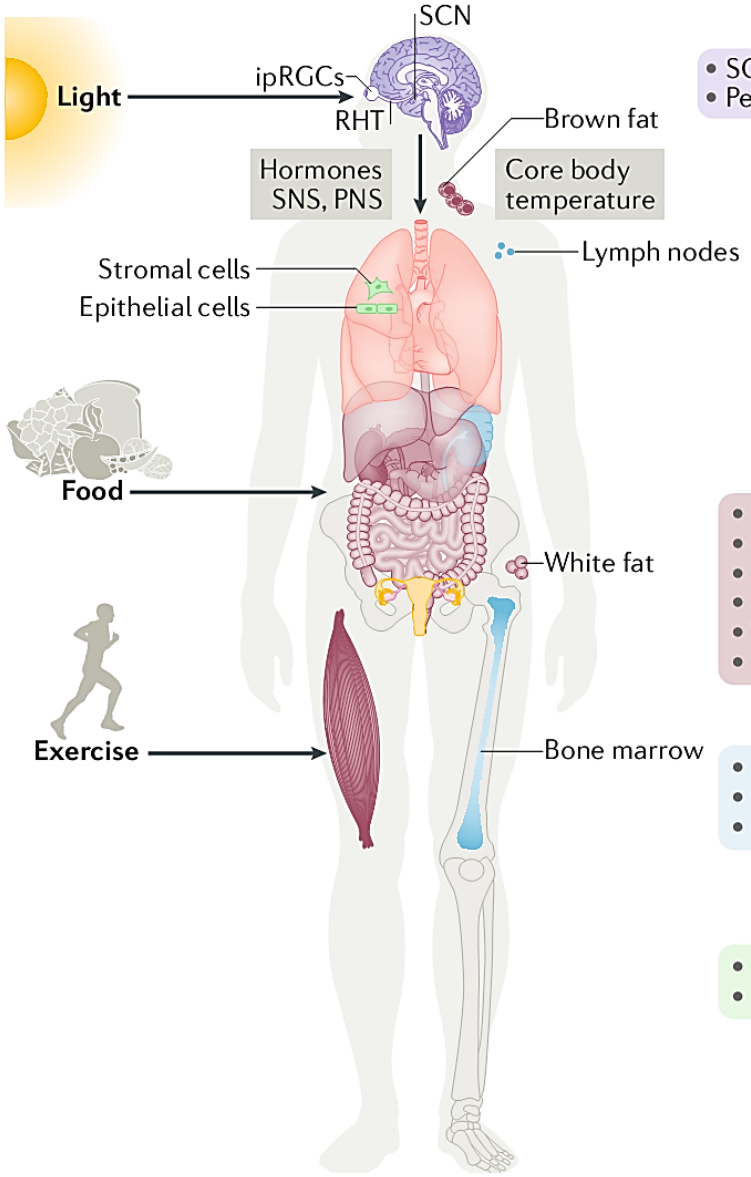
Melatonin and orexin signalling in circadian rhythm



Melatonin and orexin signalling in circadian rhythm



The peripheral clocks in humans



Nervous

- SCN (central clock)
- Peripheral brain

→

- Sleep disorders
- Mood disorders
- Neurodegenerative diseases

Cardiovascular

- Heart
- Lung

→

- Myocardial infarction
- Stroke
- Acute pulmonary oedema
- Hypertension

Metabolic

- Liver
- Pancreas
- Kidney
- Intestine
- White, brown fat
- Skeletal muscle

→

- Obesity
- Diabetes

Immune

- Lymph nodes
- Spleen
- Bone marrow

→

- Response to infection, vaccination
- Autoimmune disorders

Proliferative

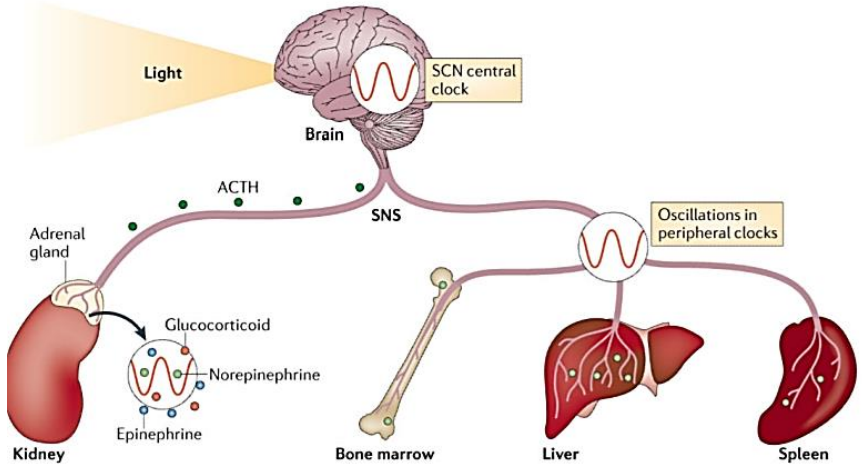
- Stromal tissue
- Epithelial tissue

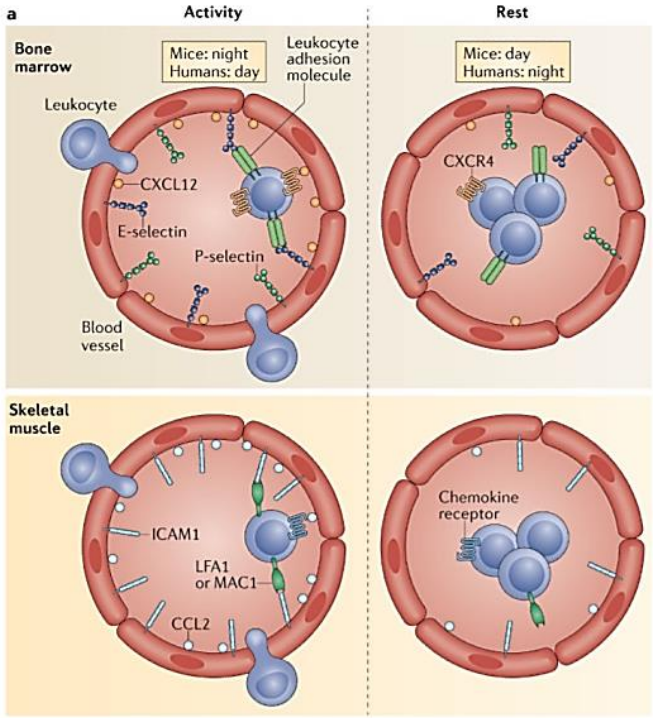
→

- Wound healing
- Cancer

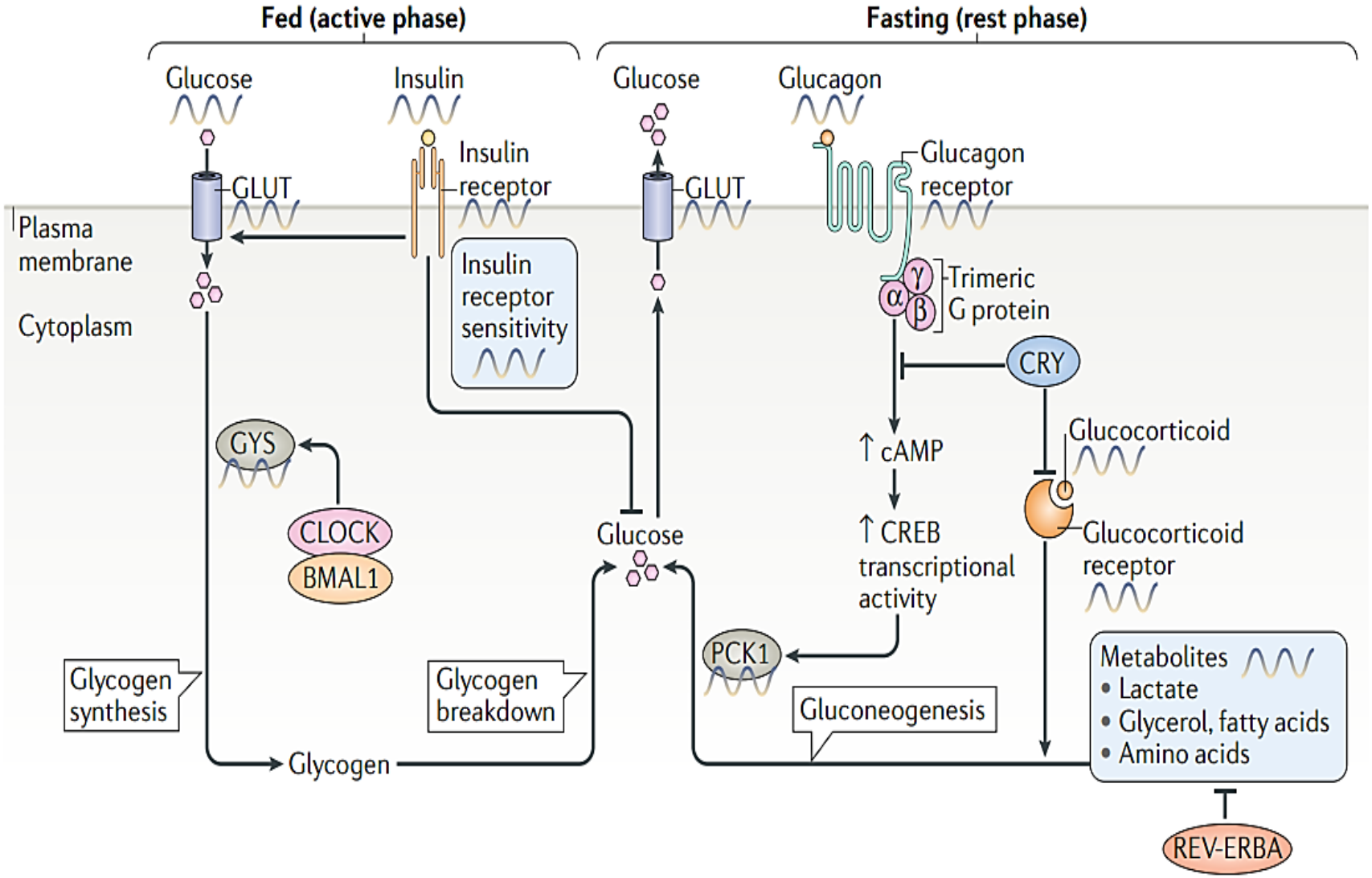
Reproductive

Ovary → Infertility





Crosstalk between metabolism and circadian clocks



Circadian Regeneration Organ Systems

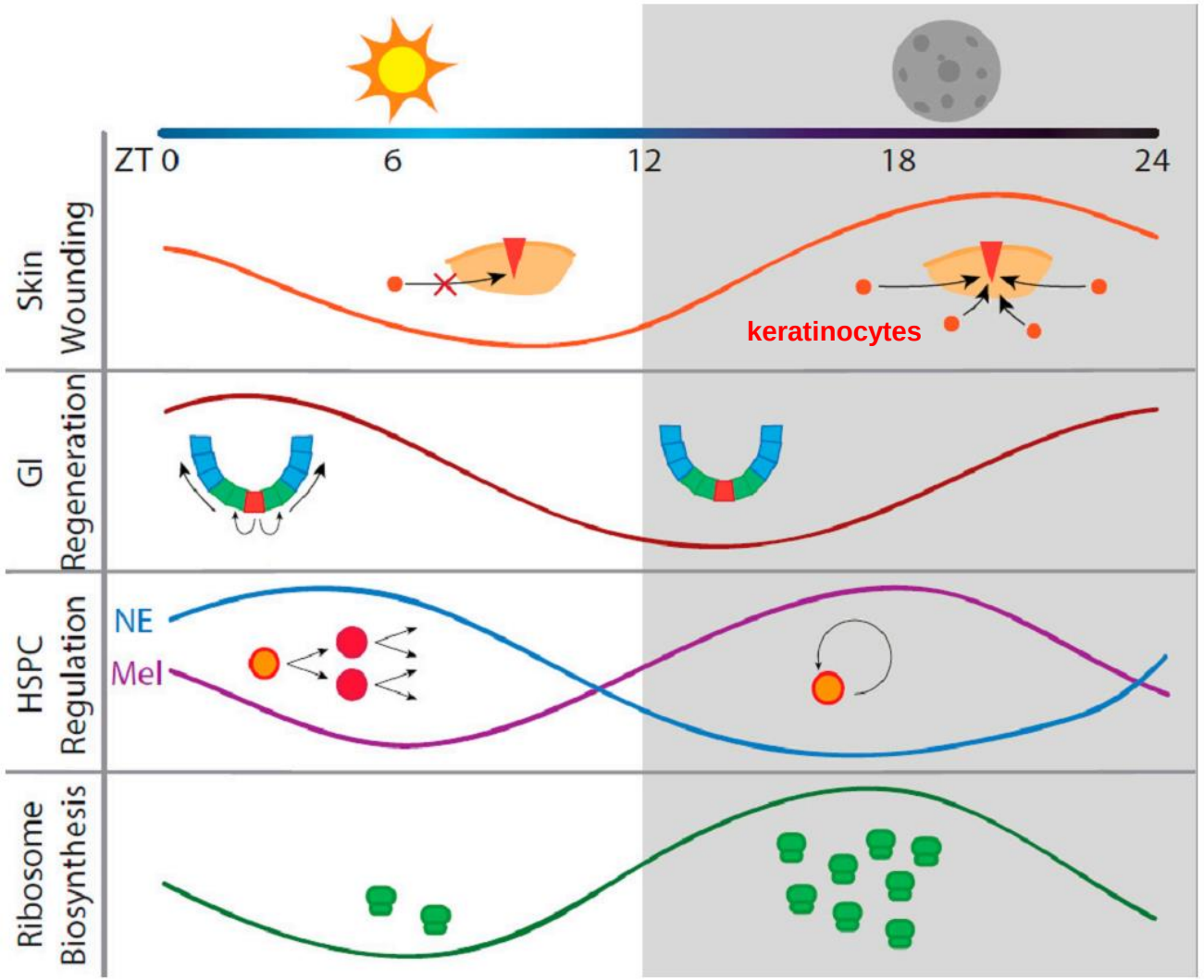
High Per2 expression correlated with increased motility and a significantly faster time to heal. This rhythmicity of wound healing efficacy also correlated with human burn healing data that showed an approximate 60% increase in the time to heal when the injury occurred during the nighttime (human resting phase) versus the daytime.

More specifically, differentiation-related genes are upregulated in “late night and early morning” while UV protection, DNA replication, and cell cycle genes are upregulated in “afternoon and evening”.

Mitotic activity of crypt cells peaked from ZT0-4 (light on from ZT0-12 and light o from ZT12-24) with a nadir of ZT12-16.

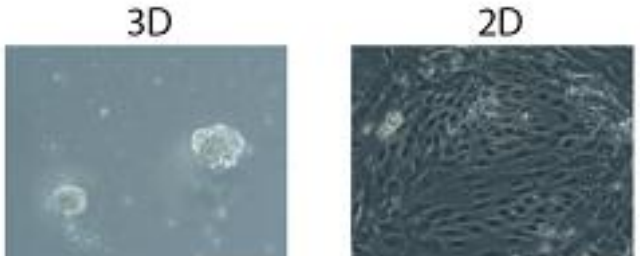
At light onset, NE and TNF secretion induce HSPC differentiation and egress through an increase in ROS levels in HSPCs (a characteristic of HSPC activation) and by increasing vascular permeability.

In mouse liver, the number of ribosomal mRNAs incorporated into polysomes, an indirect measurement of translation, was higher at night than in the morning, although the levels of the total ribosomal mRNA remained unchanged. Consistently, ribosomal protein translation and assembly occurred at night, indicating a higher capacity for protein synthesis during mouse active hours.

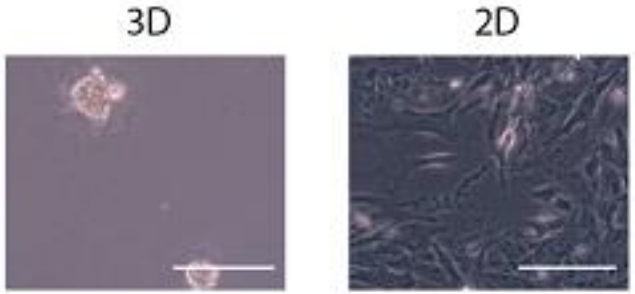


Epithelial and stromal circadian clocks are inversely regulated by their mechano-matrix environment

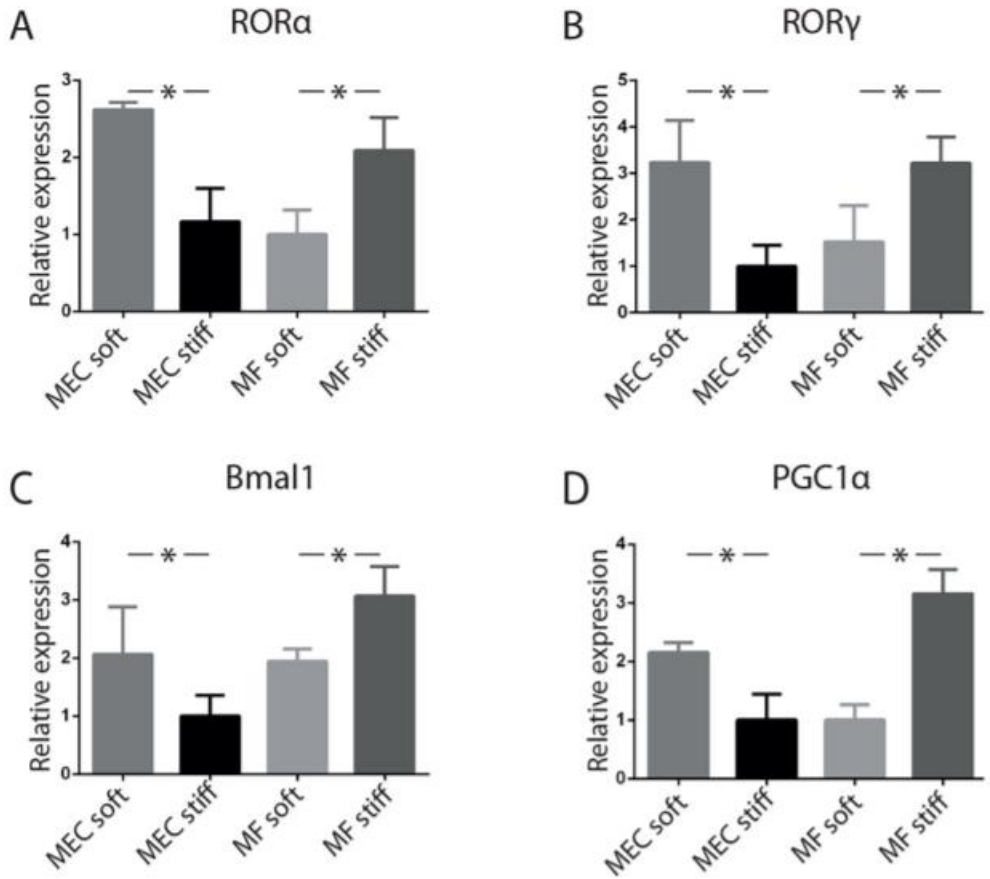
B **Epithelial cells on 3D vs 2D matrix**



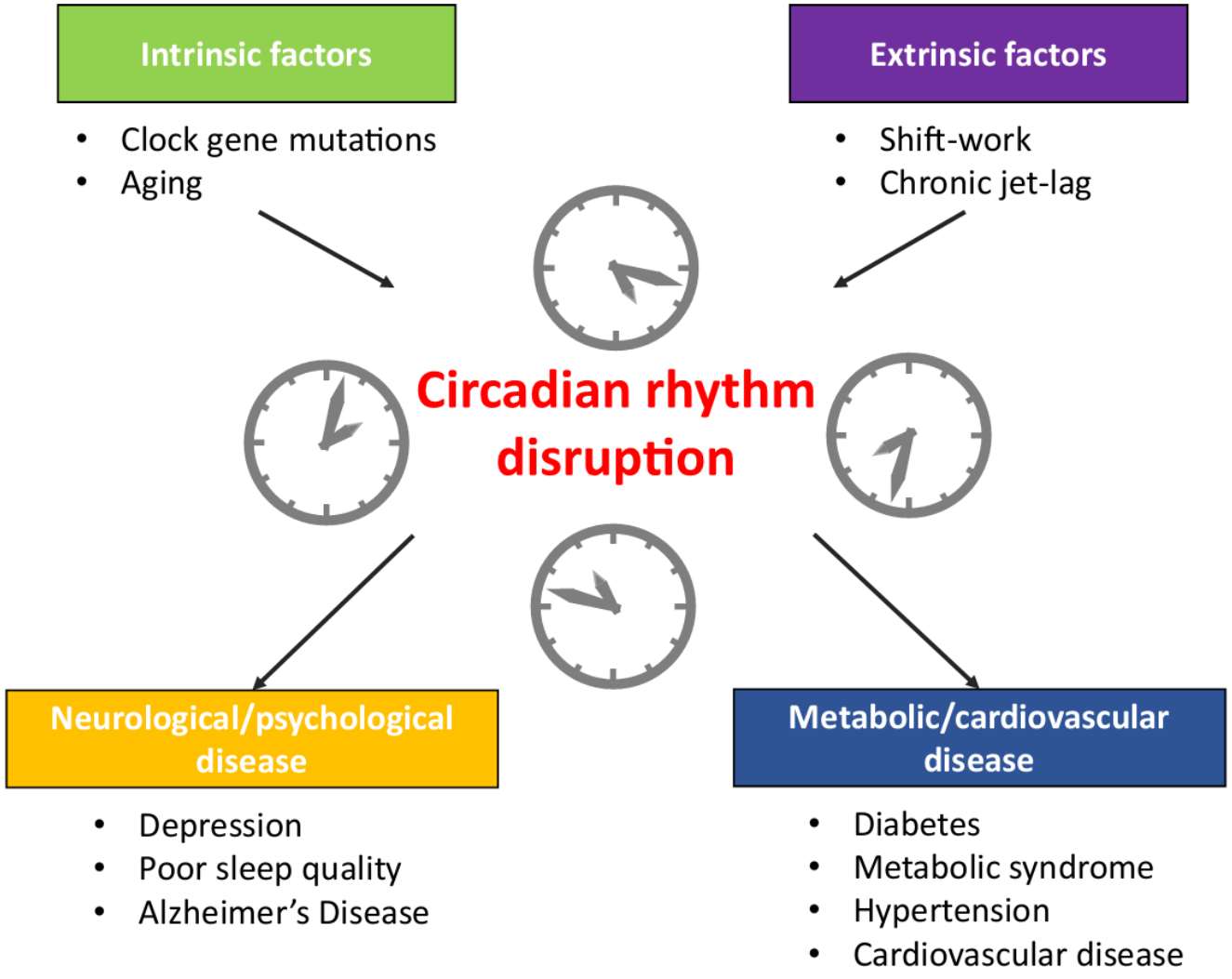
C **Fibroblasts on 3D vs 2D matrix**



Mechano-sensitivity of gene expression



Circadian Rhythms and Disease



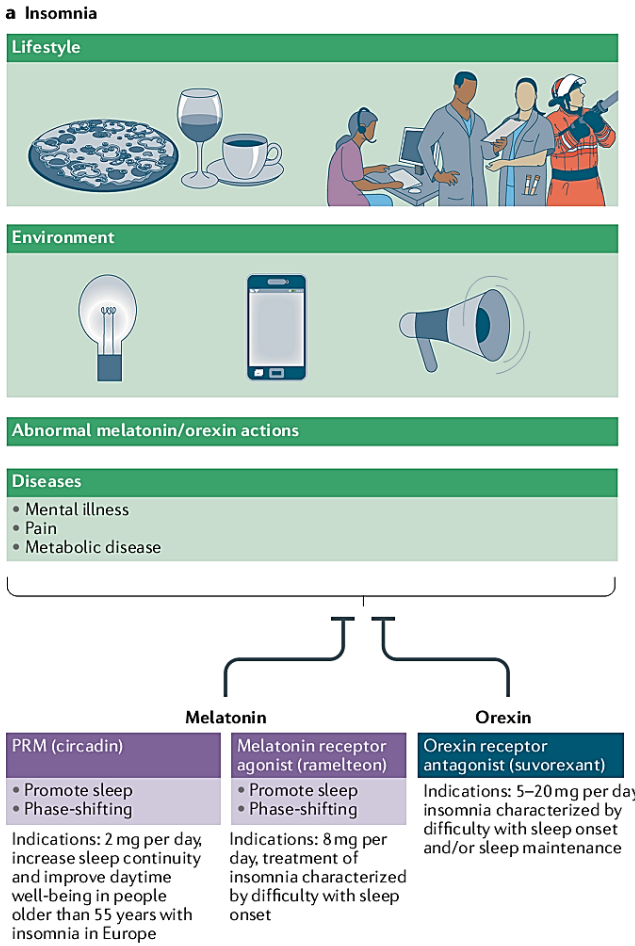
Chronotherapy and Future Prospects

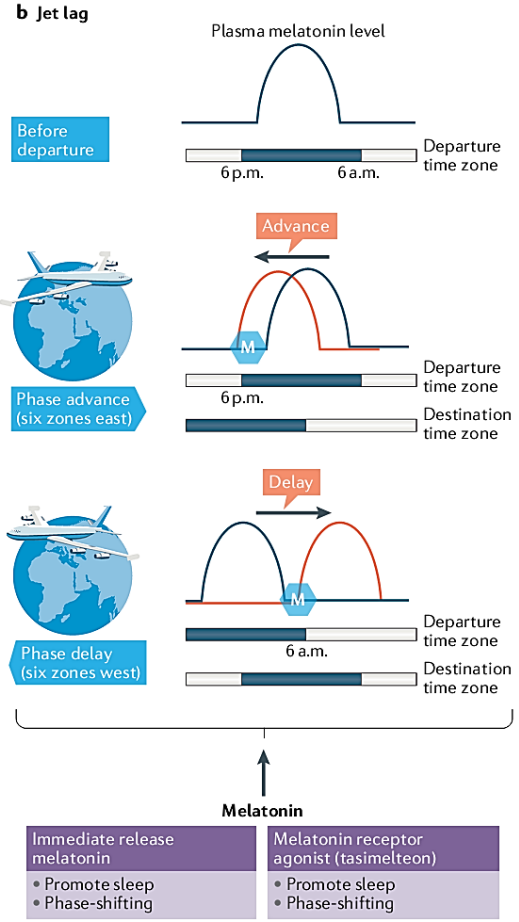
Circadian pharmacology

- Pharmacological interventions for insomnia and jet lag

Targeting the circadian machinery

Environmental and lifestyle modifications



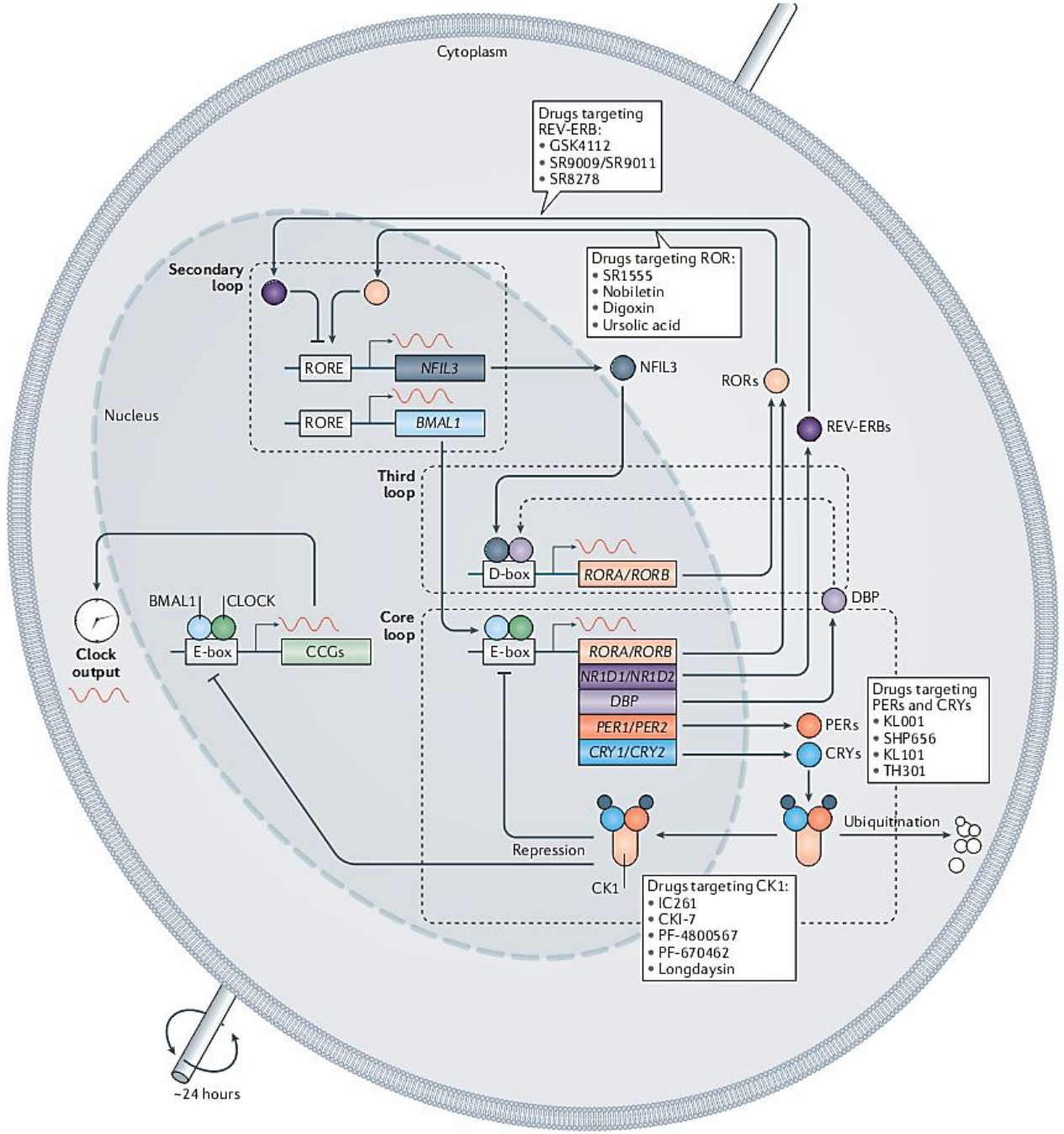


Targeting the circadian machinery

Table 2 | **Preclinical studies of small-molecule modulators targeting clock components and key regulators**

Chemical modulators	Mechanism of action	Physiological effects	Refs
CRY1/CRY2			
KL001 and CRY-stabilizing derivative (SHP656, KL101 and TH301)	Stabilize CRY, lengthen period, reduce amplitude	Improvement of glucose tolerance in obese mice, inhibition of glioblastoma stem cell proliferation in vitro, inhibition of glioblastoma tumour growth in vivo, enhancers of brown adipocyte differentiation	94,194,196,197
2-Ethoxypropanoic acid (KS15)	Inhibits CRY, activates E-box transcription, reduces amplitude	Inhibition of breast cancer cell growth	231
REV-ERBs			
GSK4112	Enhances REV-ERB and NCOR peptide interaction	Inhibition of gluconeogenesis and inflammatory response in primary cells	129,179,189
SR9009, SR9011	Derived from GSK4112, they are selective agonists for REV-ERB that alter circadian behaviour, clock gene expression (*BMAL1*, *PER1*, and *PER2*) and expression of some glioblastoma stem cell markers (for example, OLIG2 and SOX2)	Improvement of glucose homeostasis in obese mice, promotion of wakefulness, anxiolytic, inhibition of glioblastoma stem cell proliferation	94,181,183
SR8278	GSK4112-derived antagonist that increases expression of REV-ERB target genes (for example, *BMAL1*, *PCK1* and *G6PC1*) in cells	Anxiety attenuation and amelioration of myocardial injury	82,189
RORs			
Nobiletin	Agonist, enhances amplitude and lengthens period	Metabolic homeostasis improvement in obese/diabetic mice; broad efficacies with regard to inflammation and atherosclerosis	188,232,233
Neoruscogenin	Agonist promoting ROR interaction with NCOA2/TIF2, activates BMAL1 expression	Activation of hepatic expression of ROR metabolic target genes	234
SR1001	Derived from T0901317 with high inverse agonist activity and selectivity for RORα and RORγt	Inhibition of T_H17 cell differentiation and autoimmunity	193
SR2211, SR1555, digoxin, ursolic acid, ML209	RORγ inverse agonist	Inhibition of T_H17 cell differentiation	189,191,192
SR3335	RORα inverse agonist	Reduction of blood glucose level in obese mice	235
SR1078	RORα agonist	Induction of apoptosis and inhibition of hepatoma cell growth	236
CK1 kinases			
CKI-7, IC261, D4476, PF-670462, PF-4800567 longdaysin, LH846, compounds 1–3 among others	Inhibitors, lengthen period	Pharmacological inhibition of CK1, significantly lengthen circadian rhythms mainly by nuclear retention of PER2. CK1 is broadly involved in various pathophysiologies, including familial sleep and mood disorders	199–201,237
PER2			
Lithium	Increased transcription of *PER2*, lengthens period and enhances amplitude of PER2 rhythms	Treatment of bipolar disorder associated with circadian rhythm disruptions	239

Targeting the circadian machinery



Environmental and lifestyle modifications

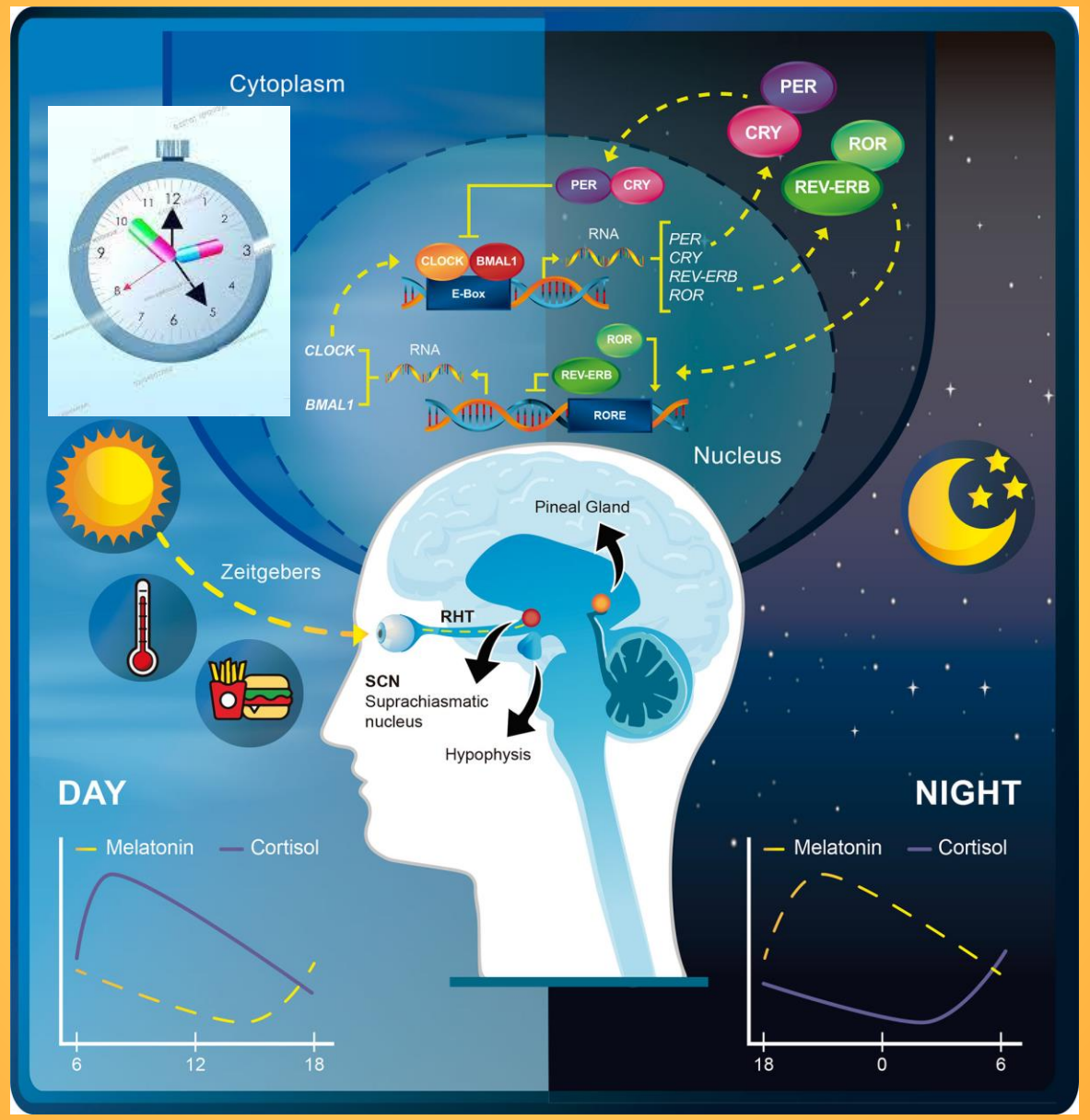
- Blue light is a dominant zeitgeber, and the pervasive night-time light exposure in modern societies interferes with neuroendocrine circuits to perturb sleep and dampen rhythms of melatonin and cortisol.
- Conversely, bright light therapy, commonly conducted by exposure to broad-spectrum bright light (2,000–10,000 lux) for 1–3 hours in the morning, can improve sleep–wake cycles, mood and cognitive functions in patients with sleep or seasonal affective disorders.
- For example, time-restricted feeding (TRF), characterized by food access for 8–9 hours during the active phase, has been found to exert strong preventive and therapeutic effects in metabolic disorders.
- Temporally controlled activity has also been studied in laboratory and clinical settings. In humans, exercise and activity can reset circadian melatonin rhythms, and afternoon exercise has been found to improve sleep quality in older people.

Table 3 | **Clinical trials involving behavioural and environmental modifications**

Modifications	Disease indications	Parameters	Examples
Light therapy	Stroke, ageing, Parkinson disease, Alzheimer disease, mood disorders, metabolic disease, night shift, PTSD, traumatic brain injury, sepsis, cancer-related fatigues	Circadian rhythms in sleep and blood parameters, cognition, activity, fatigue, depression and PTSD scores, inflammation markers	NCT02186392
			NCT02502045
			NCT02769858
			NCT01855126
			NCT01048294
			NCT01747811
Time-restricted feeding	Obesity, metabolic syndrome, shiftwork	Body weight, metabolic homeostasis, cardiometabolic parameters	NCT02204735
			NCT03527290
Sleep intervention	Night-shift work, traumatic brain injury	Sleep quality	NCT02838082
			NCT02609373
Scheduled activity	Diabetes, Alzheimer disease	Sleep, glucose homeostasis	NCT03553524
			NCT01920672
Combination: including sleep, light, exercise and lithium	Night-shift work, HIV-related fatigue, mood disorders, ICU stay	Circadian phase, sleep, metabolic parameters, mood rating, clock gene expression	NCT01284140
			NCT01767181
			NCT02126007
			NCT01799733
			NCT03405493
			NCT01431573

ICU, intensive care unit; PTSD, post-traumatic stress disorder.

Conclusion


Cytoplasm
PER
CRY
ROR
REV-ERB
PER
CRY
CLOCK
BMAL1
E-Box
RNA
PER
CRY
REV-ERB
ROR
CLOCK
BMAL1
RNA
ROR
REV-ERB
RORE
Nucleus
Pineal Gland
Zeitgebers
RHT
SCN
Suprachiasmatic
nucleus
Hypophysis
DAY
Melatonin
Cortisol
6
12
18
NIGHT
Melatonin
Cortisol
18
0
6