University of Zurich[UZH]

Circadian Regulation

2.10.2018

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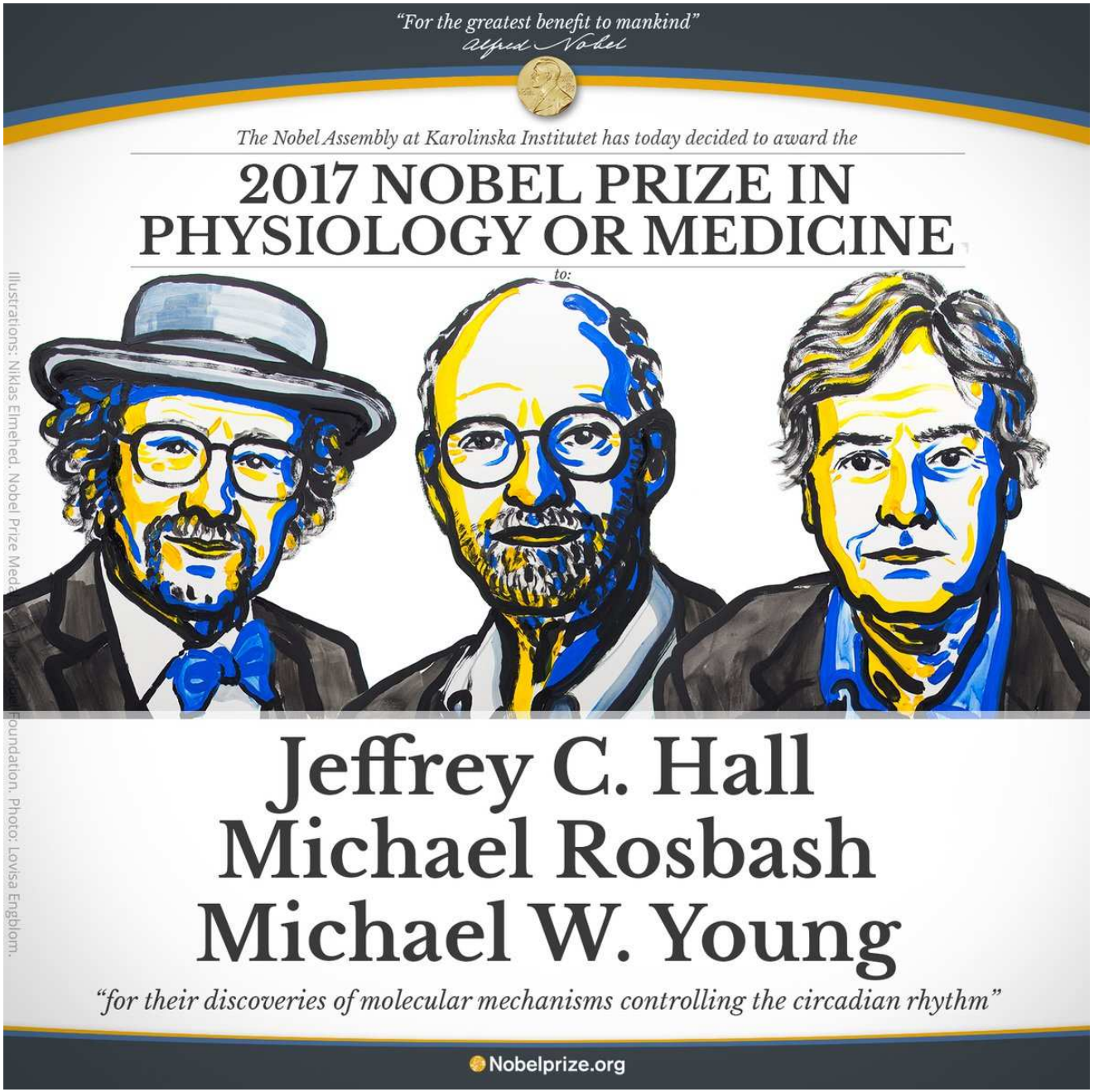
University of Zurich

2017 Nobel Prize in Physiology or Medicine



2017 Nobel Prize in Physiology or Medicine

Here's what the Nobel Foundation has to say about the prize for understanding the body's inner clock:

- Life on Earth is adapted to the rotation of our planet. For many years we have known that living organisms, including humans, have an internal, biological clock that helps them anticipate and adapt to the regular rhythm of the day. But how does this clock actually work? Jeffrey C Hall, Michael Rosbash and Michael W Young were able to peek inside our biological clock and elucidate its inner workings. Their discoveries explain how plants, animals and humans adapt their biological rhythm so that it is synchronized with the Earth's revolutions.

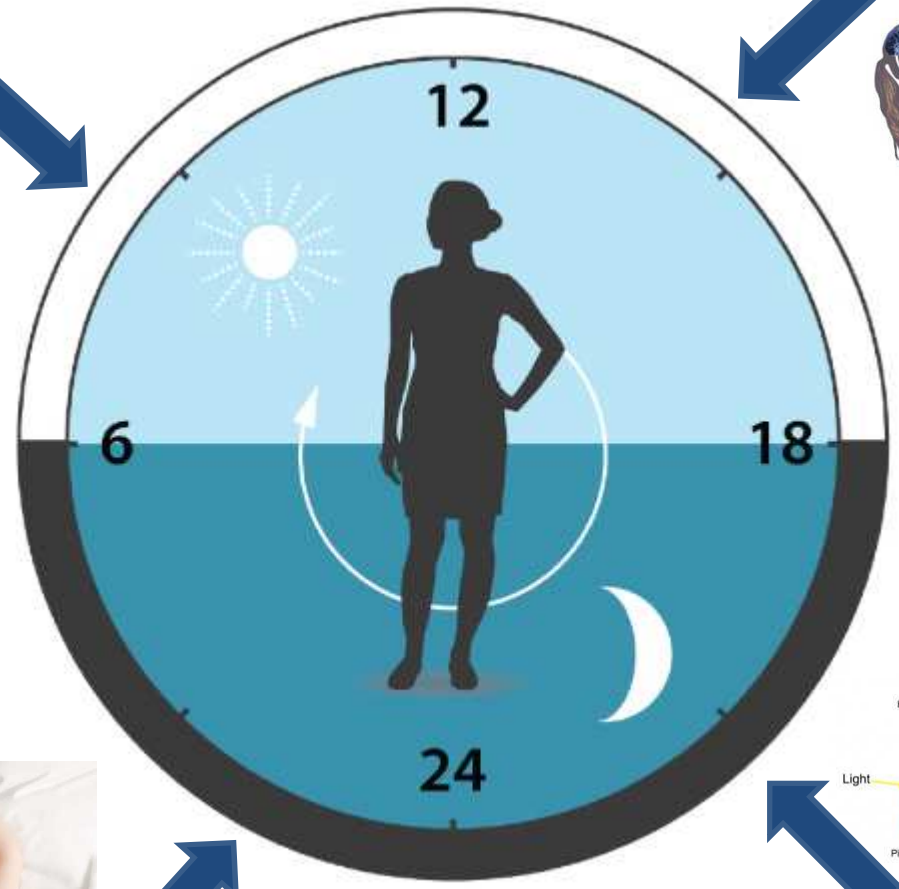
Circadian Regulation

- Circadian Rhythm
- Mammalian Circadian System
  - Entrainment: Light and More
  - Central Pacemaker: SCN
  - A Transcriptional Feedback Loop
  - Output Pathways: Melatonin and more
  - Peripheral Oscillators
- Circadian Clock Related Disease

Circadian Rhythm

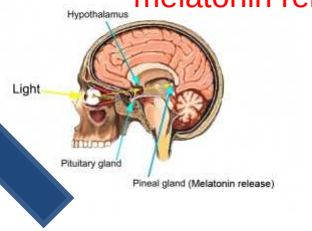
Physical, Mental and Behavioral Changes that Follow a Roughly 24-hour Cycle

9am shit time



highest reaction time and coordination maximum performance

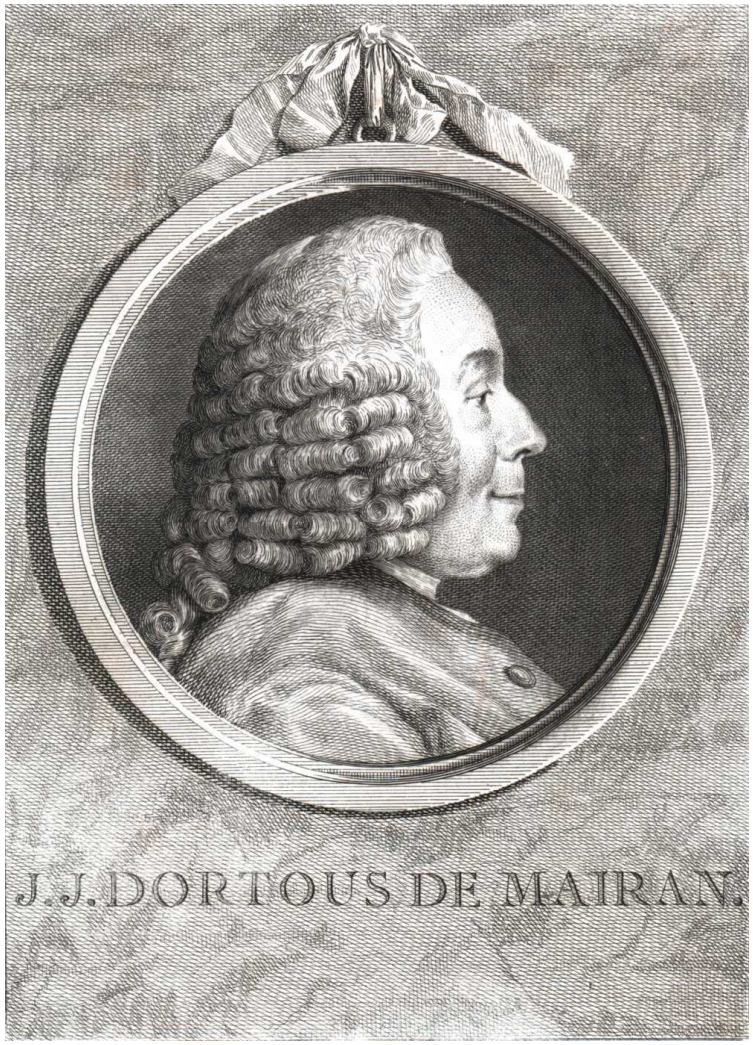
melatonin release at 9 pm

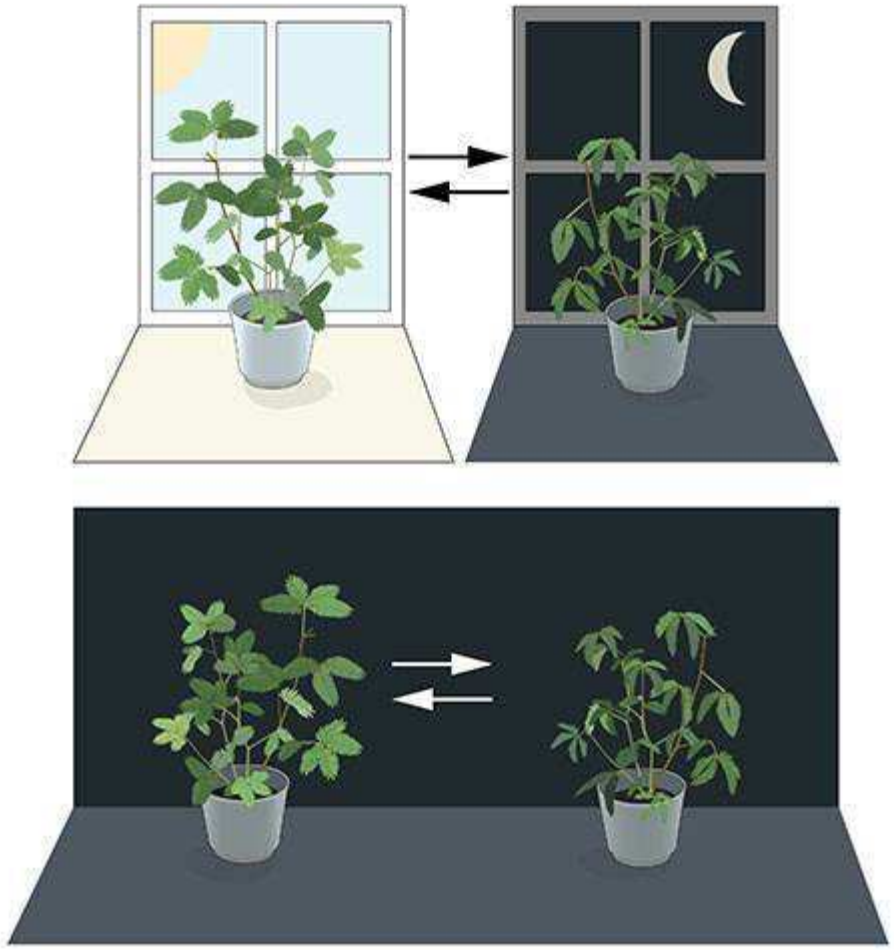


2am deepest sleep

Circadian Rhythm: A Day in the Body

Endogenous Timing System





1729

A Brief History of Biological Time

1729	Publication by Jacques d'Ortous de Mairan on the movements of Mimosa leaves in constant darkness
1751	Carl Linnaeus presented his "flower clock" in his *Philosophia botanica*, to estimate time of day according the timing of open and closed flowers in the field
1759	Du Monceau demonstrated that the rhythm in leaf movement is independent of temperature fluctuations
1832	Augustine De Candolle reported the presence of a circadian (22 h) period of leaf movement
1880	Charles Darwin published "The power of movement in plants," including an analysis of "sleep movements of leaves"
1920s and 1930s	Studies by E. Bünning on the heitability of circadian rhythms
1920s	Description of endogenous circadian rhythms in the rat (C. Richter)
1950s	Formal properties of biological rhythms (C. Pittendrigh)
1959	Franz Halberg coins the name "circadian"
1960	C. Pittendrigh and J. Aschoff organize the first Cold Spring Harbor Symposium on Biological Clocks
1960s	Analysis of human circadian rhythms in temporal isoloation (J. Aschoff)
1968	Complete description of a biological clock in the avian pineal gland (M. Menaker)
1971	Discovery of the per mutation in *Drosophila* (R. Konopka, S. Benzer)
1972	Role of the suprachiasmatic nuclei in circadian rhythmicity (I. Zucker, R. Moore)
1976	C. Pittendrigh and S. Daan publish a series of papers on the experimental and formal basis of circadian rhythms in rodents
1984	Cloning of the per gene in *Drosophila*
1988	Discovery of the tau mutation in the hamster
1990s	Description of a transcription-translation negative-feedback model of the circadian clock in several species; cloning of clock genes
1994	Creation of the *clock* mouse mutant
1998–2000	Discovery of the cellular and physiological basis of nonvisual photoreception in mammals; description of peripheal circadian clocks
2000	Cloning of the tau mutation in hamsters
2000s	Annotation of the circadian transcriptome

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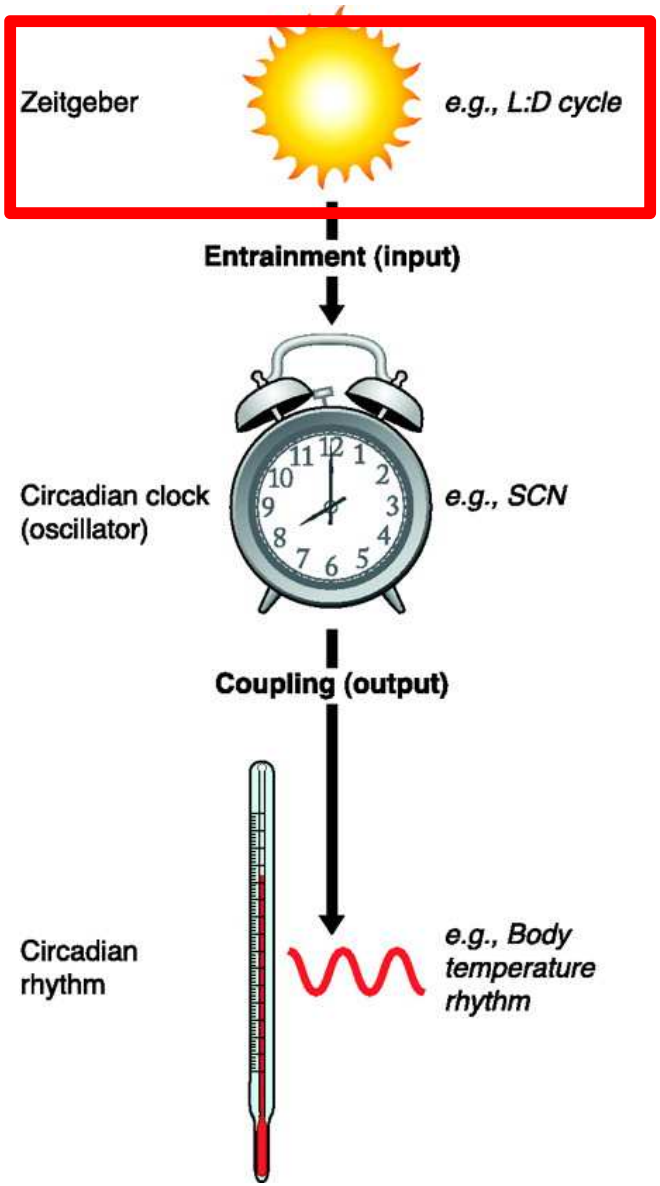
Mammalian Circadian System

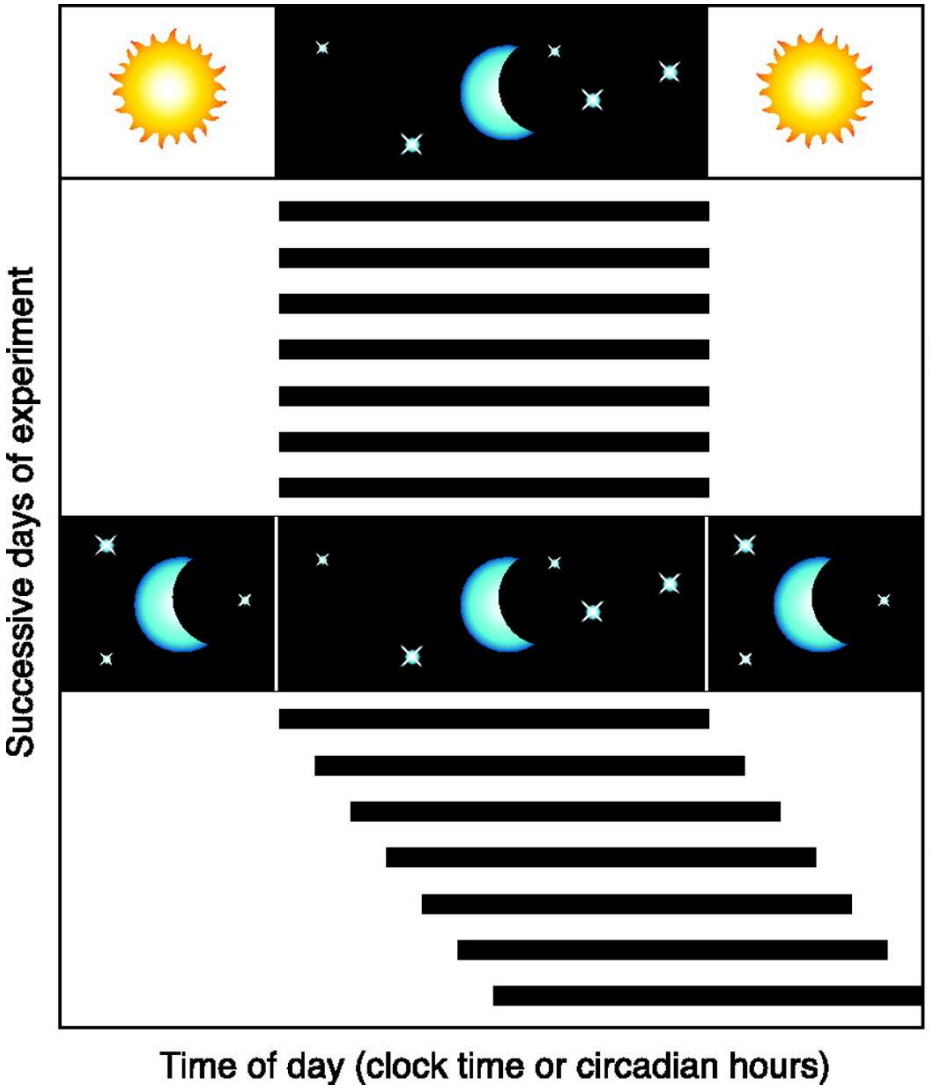
- How does Clock Interact with the Environment?
- Where is the Clock and How does it Work?
- How does the Clock Tell Time to the Rest of the Body?

How does Clock Interact with the Environment?



Diego A. Golombek and Ruth E. Rosenste, 2010

Light is the Dominant Entraining Stimulus

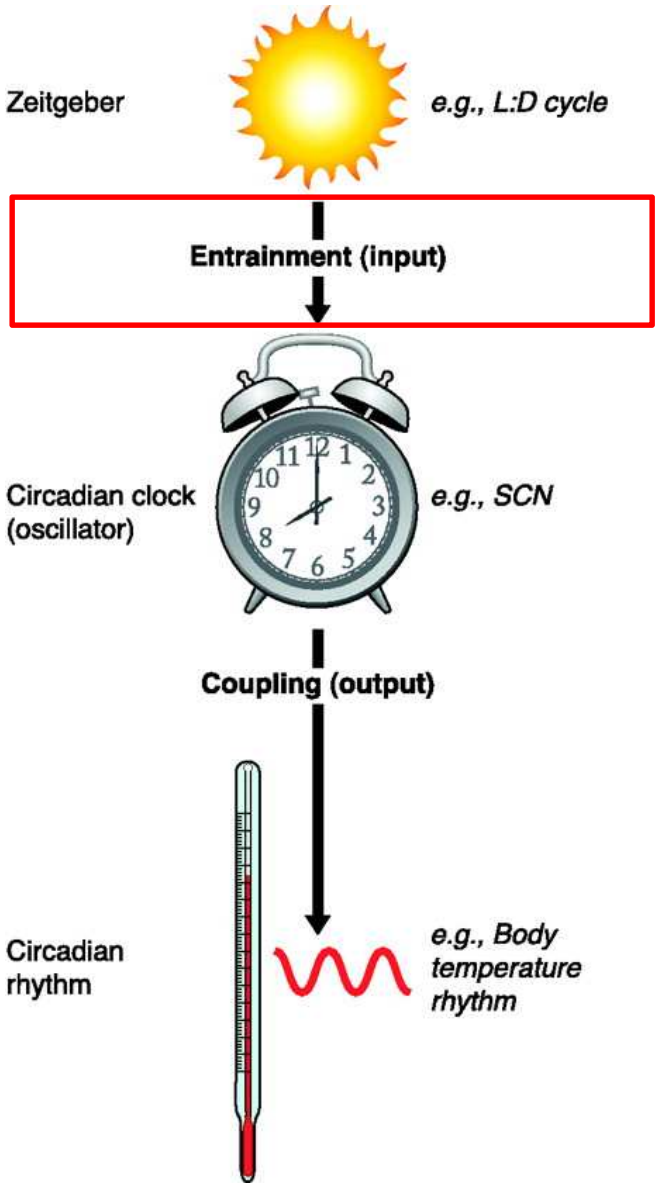


Other Zeitgeber: Food, caffeine, exercise…….

free-running: the circadian clock is changed to a later time point, but it is retained

Diego A. Golombek and Ruth E. Rosenste, 2010

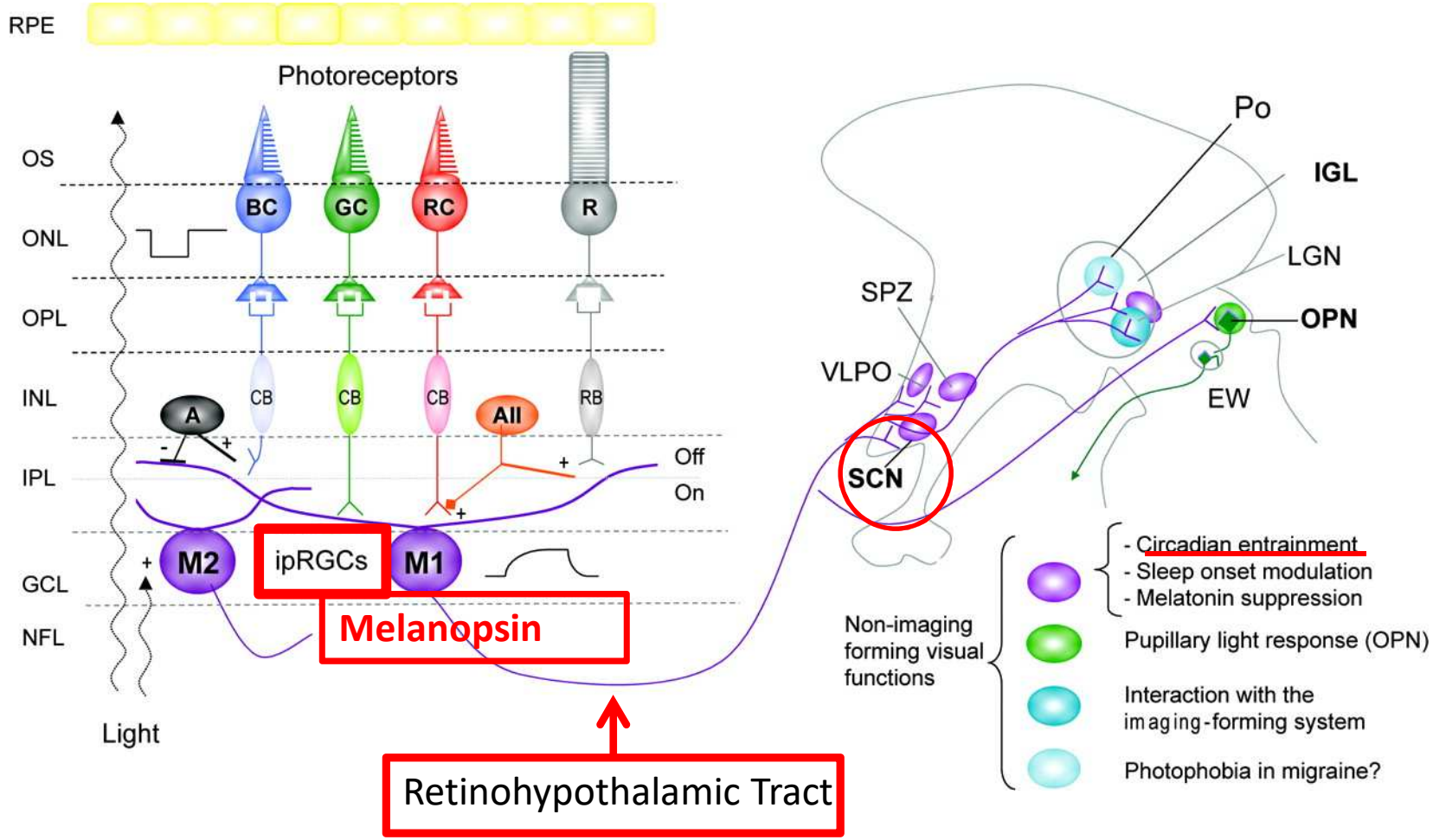
How does Clock Interact with the Environment?



Diego A. Golombek and Ruth E. Rosenste, 2010

Light Entrainment in Mammals

Intrinsically Photosensitive Retinal Ganglion Cells (ipRGCs)



light trigger possible, becuse ipRGCs also are light sensitivie with melanopsin that signals to SCN. blind people also have circ clock. not used for vision itself. ipRGCs are a thrid type of photoreceptors ,though they play role in vision formation

Eduardo E. Benarroch Neurology 2011;76:1422-1427

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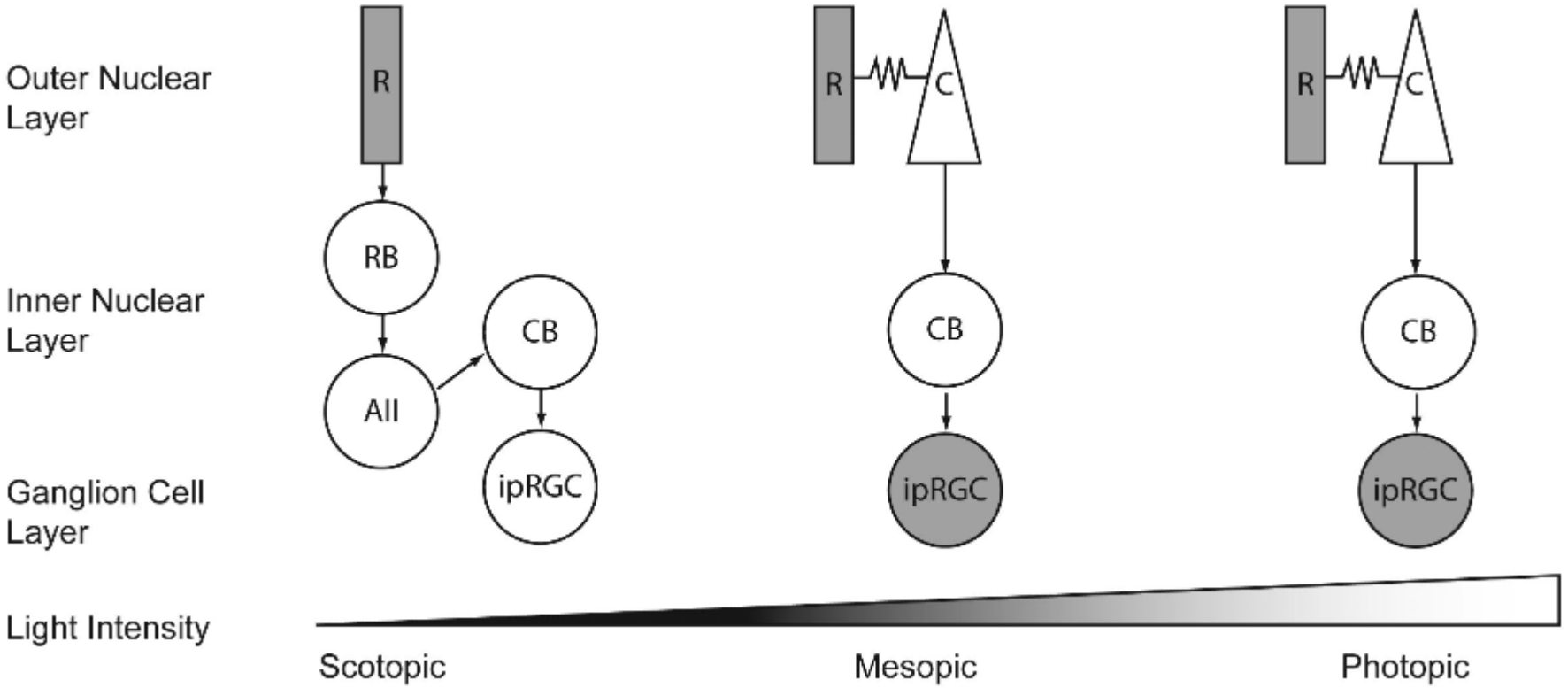
Rods Drive Circadian Photoentrainment

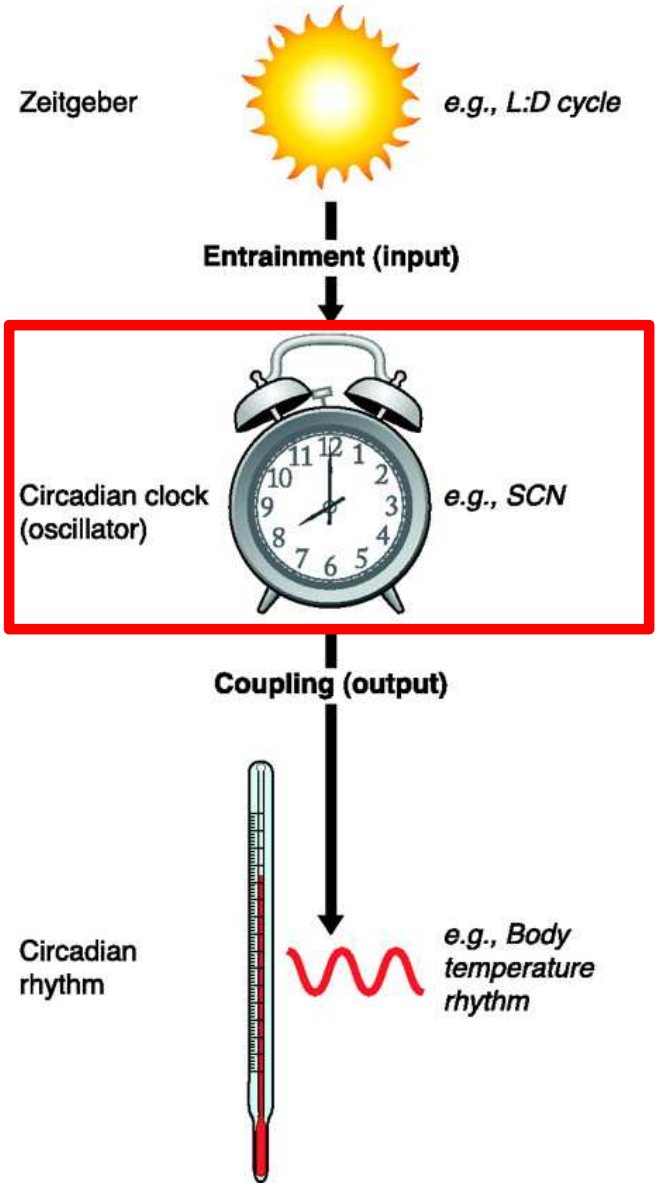
melanopsin not that senstivi, cannot be activated in darkness. rod is though, since it can register 1-2 quanta of light



these are two different circuits to induce photoentrainment.

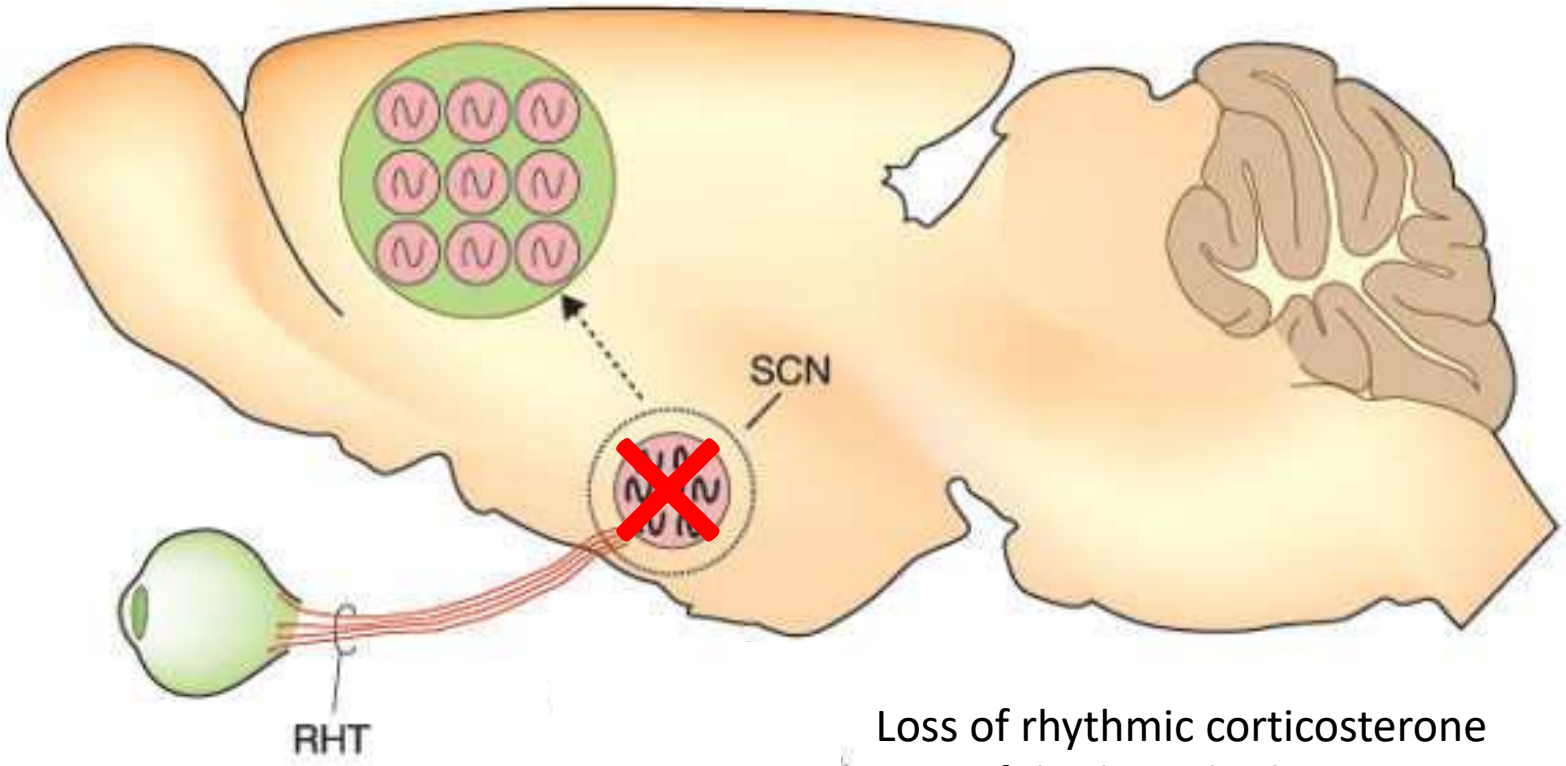
Altimus C et al 2010

Where is the Clock and How does it Work?



Diego A. Golombek and Ruth E. Rosenste, 2010

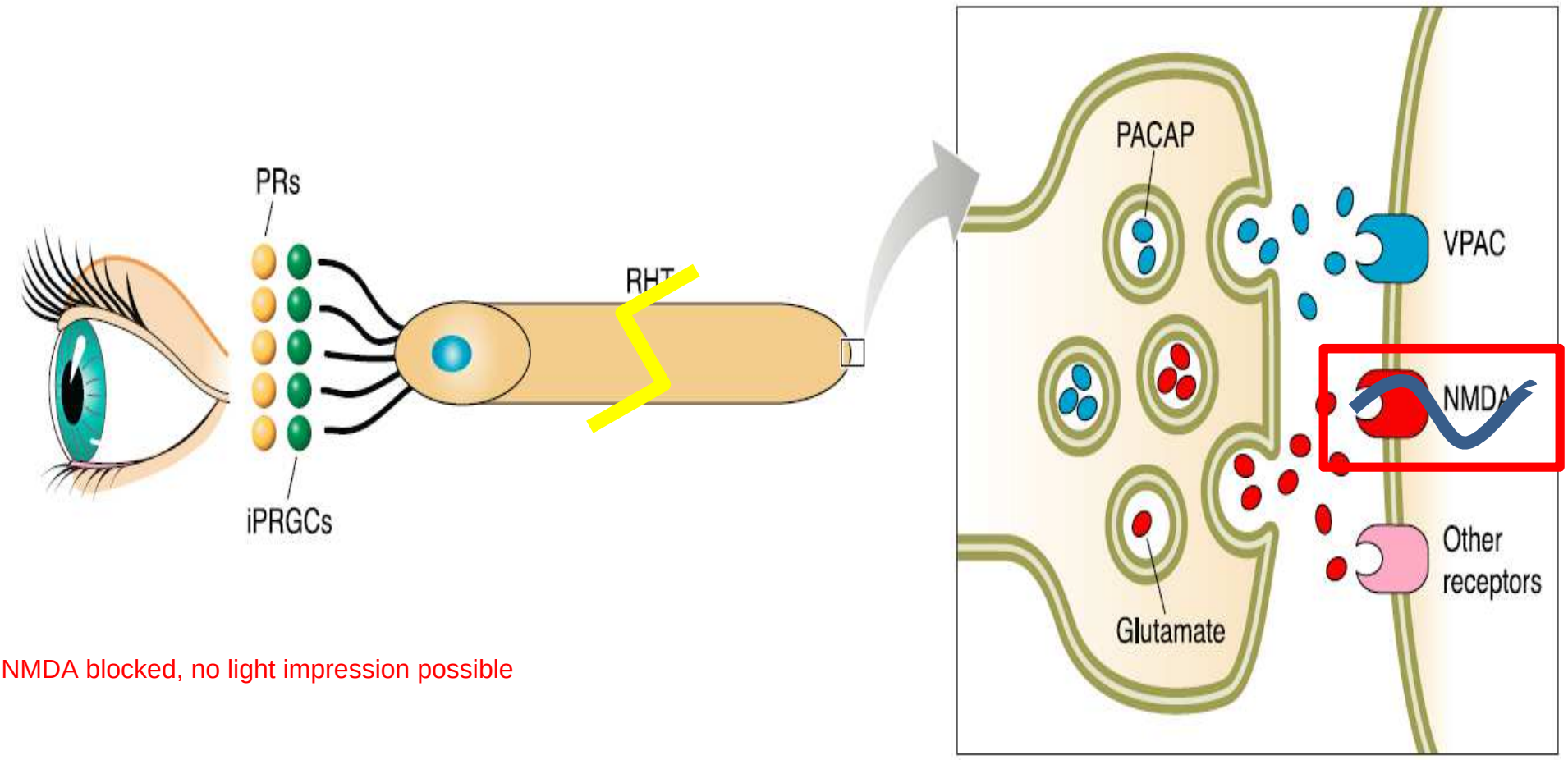
SCN------ the Central Pacemaker



Loss of rhythmic corticosterone
Loss of drinking rhythm

Steven M. Reppert & David R. Weaver 2002

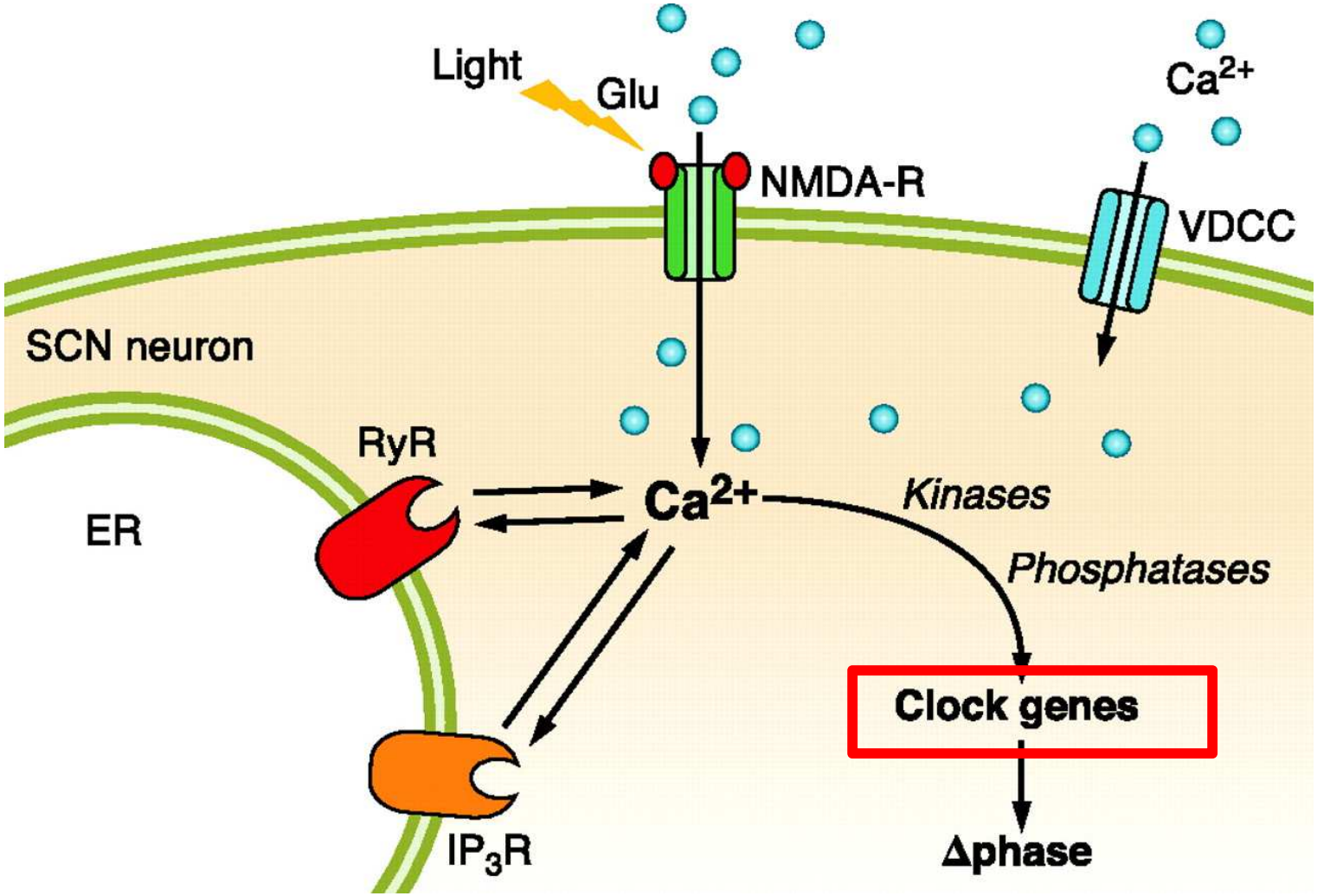
Glutamate is the Main Photic Signal



if NMDA blocked, no light impression possible

Diego A. Golombek, and Ruth E. Rosenstein Physiol Rev 2010;90:1063-1102

Signal Transduction in SCN



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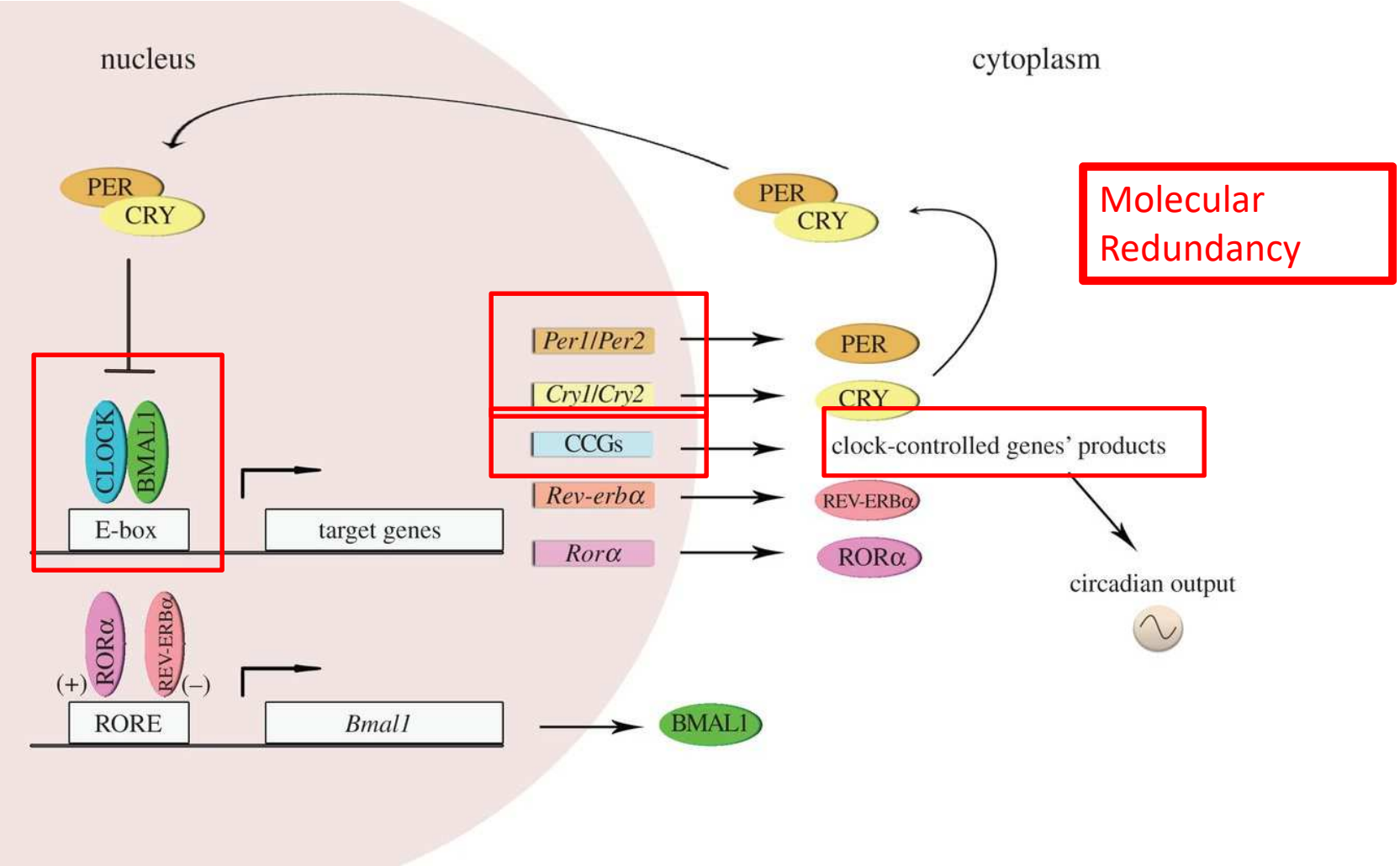
A Transcriptional Feedback Loop



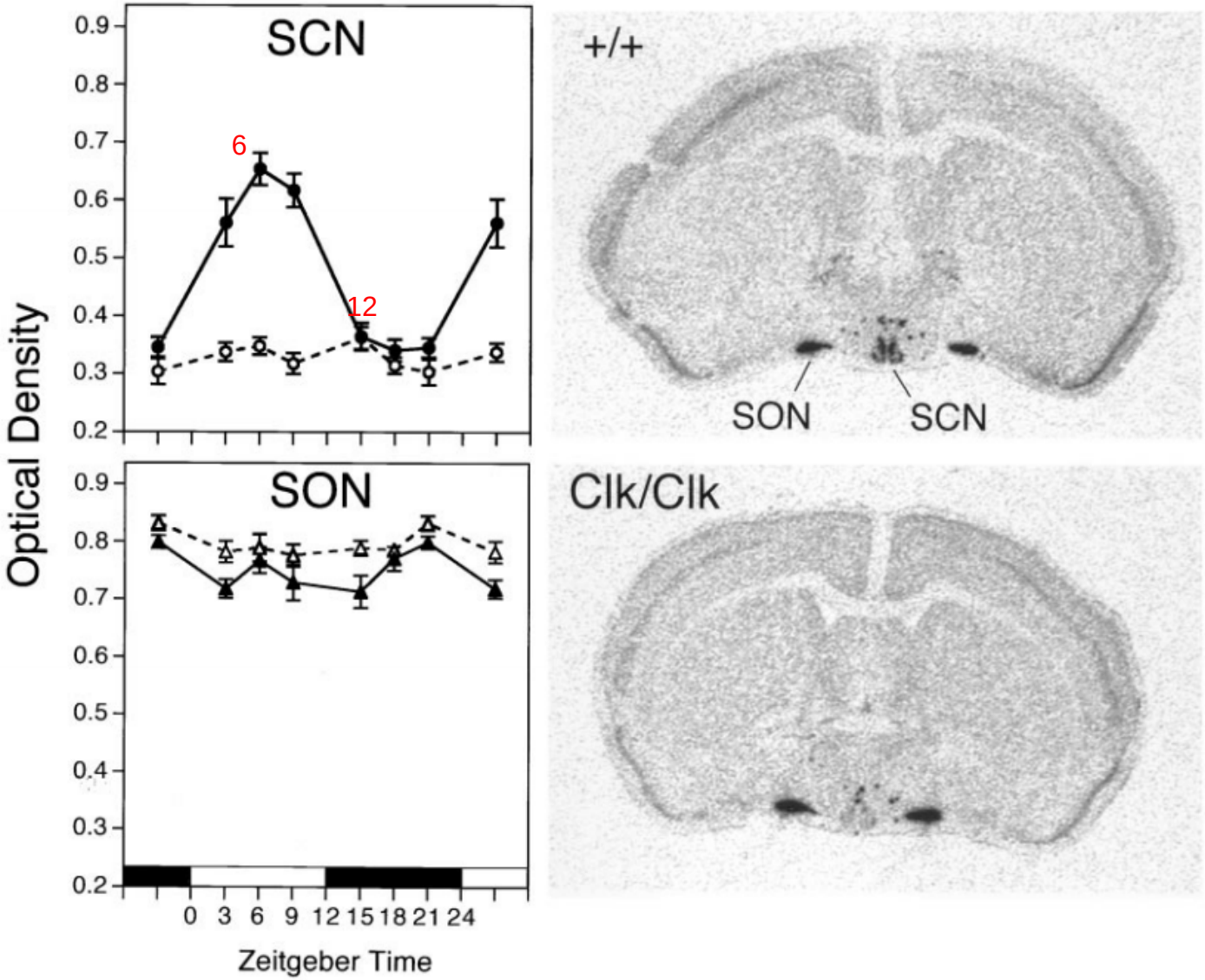
Diego A. Golombek et al. Phil. Trans. R. Soc. B 2014;369:20120465

PER-CRY goes to nucleus and inhibits CLOCK AND BAML1 to inhibit E-Box, s.t. PER and CRY transcrption is inhibited. this is a 24h rhythm happening

AVP hormone expressed in hypothalamus

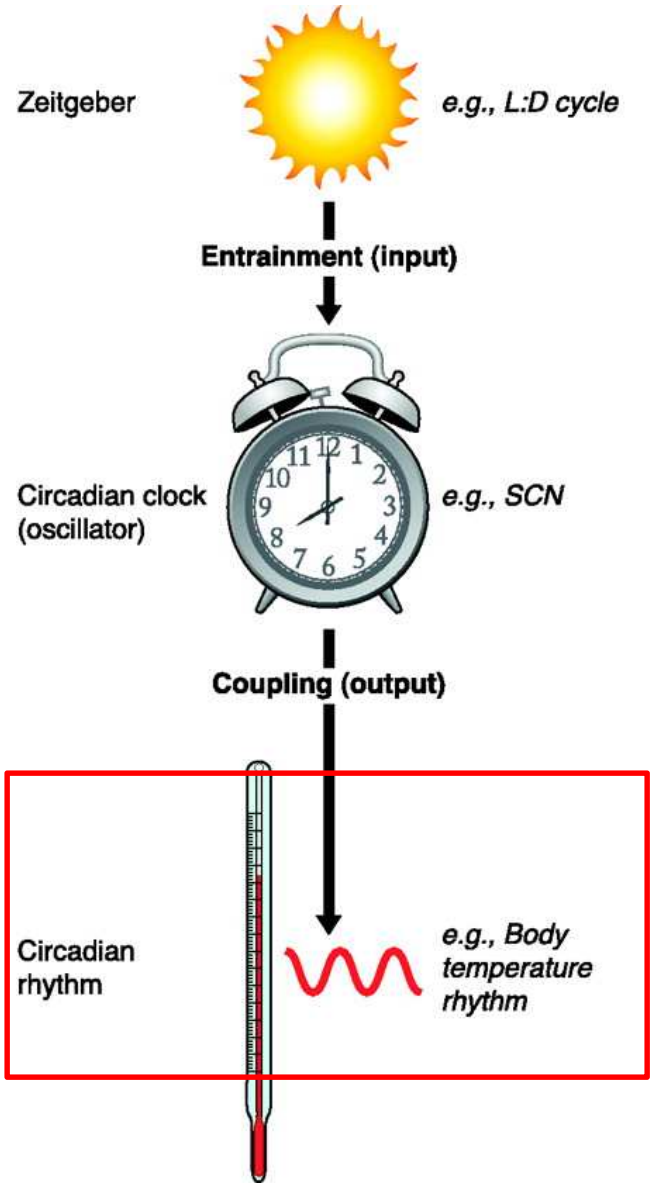
Clock-Controlled Genes

e.g.Arginine Vasopressin (AVP)



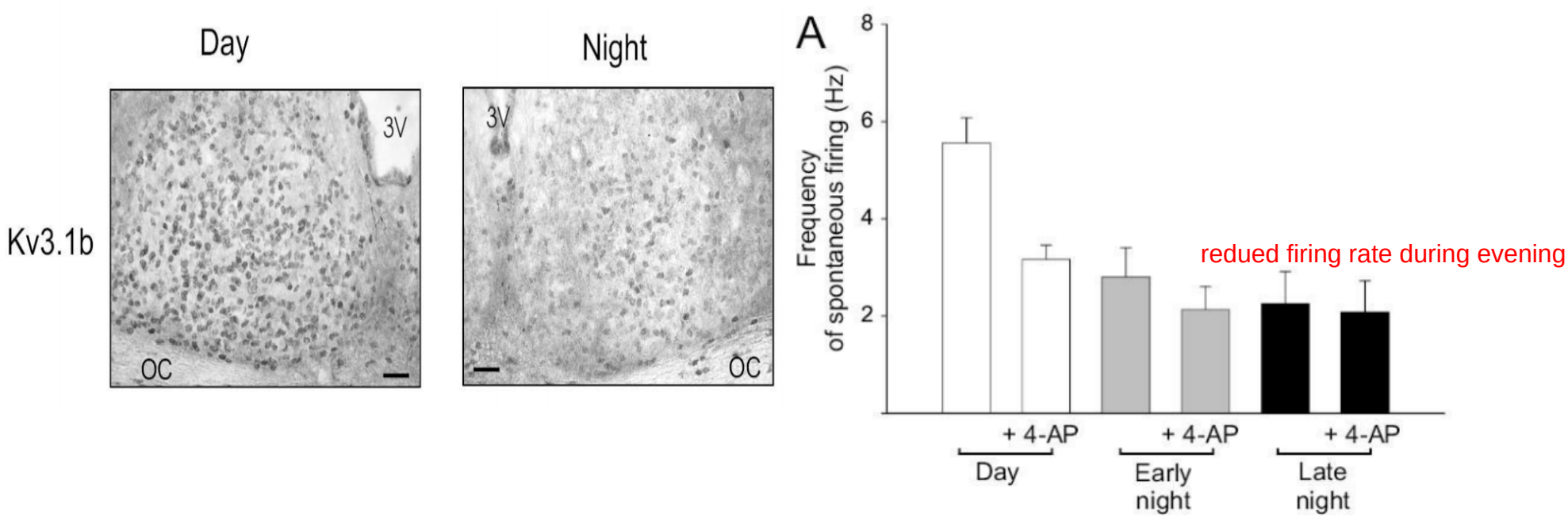
Jin et al, 1999

How does the Clock Tell Time to the Rest of the Body?



Diego A. Golombek and Ruth E. Rosenste, 2010

From Molecular Feedback Loop to Firing Rate Rhythms

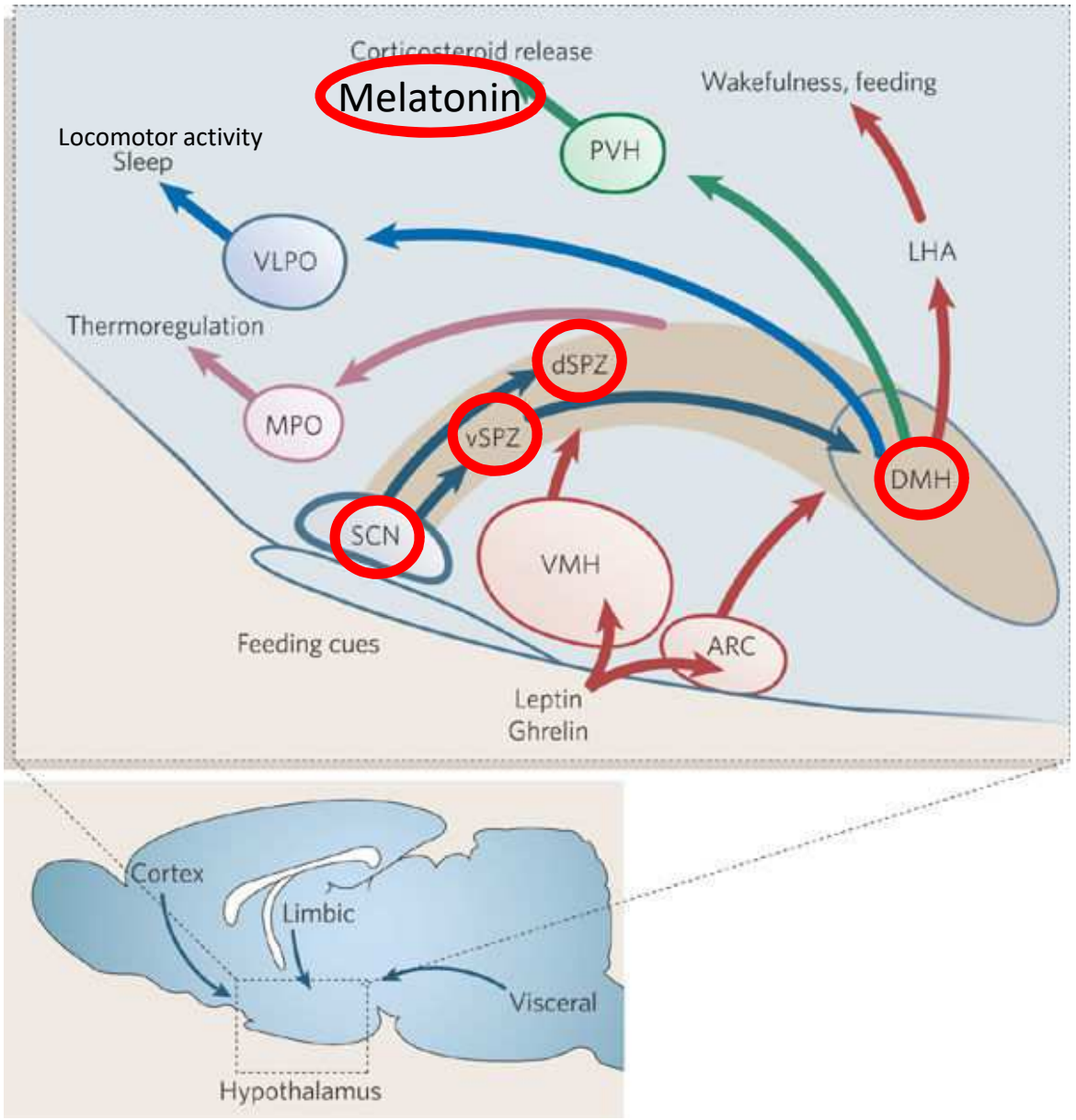


Itri et al 2005

body temp highest at evening. it depends where projection occurs (look closely at arrows)

Circadian Clocks Output Pathways

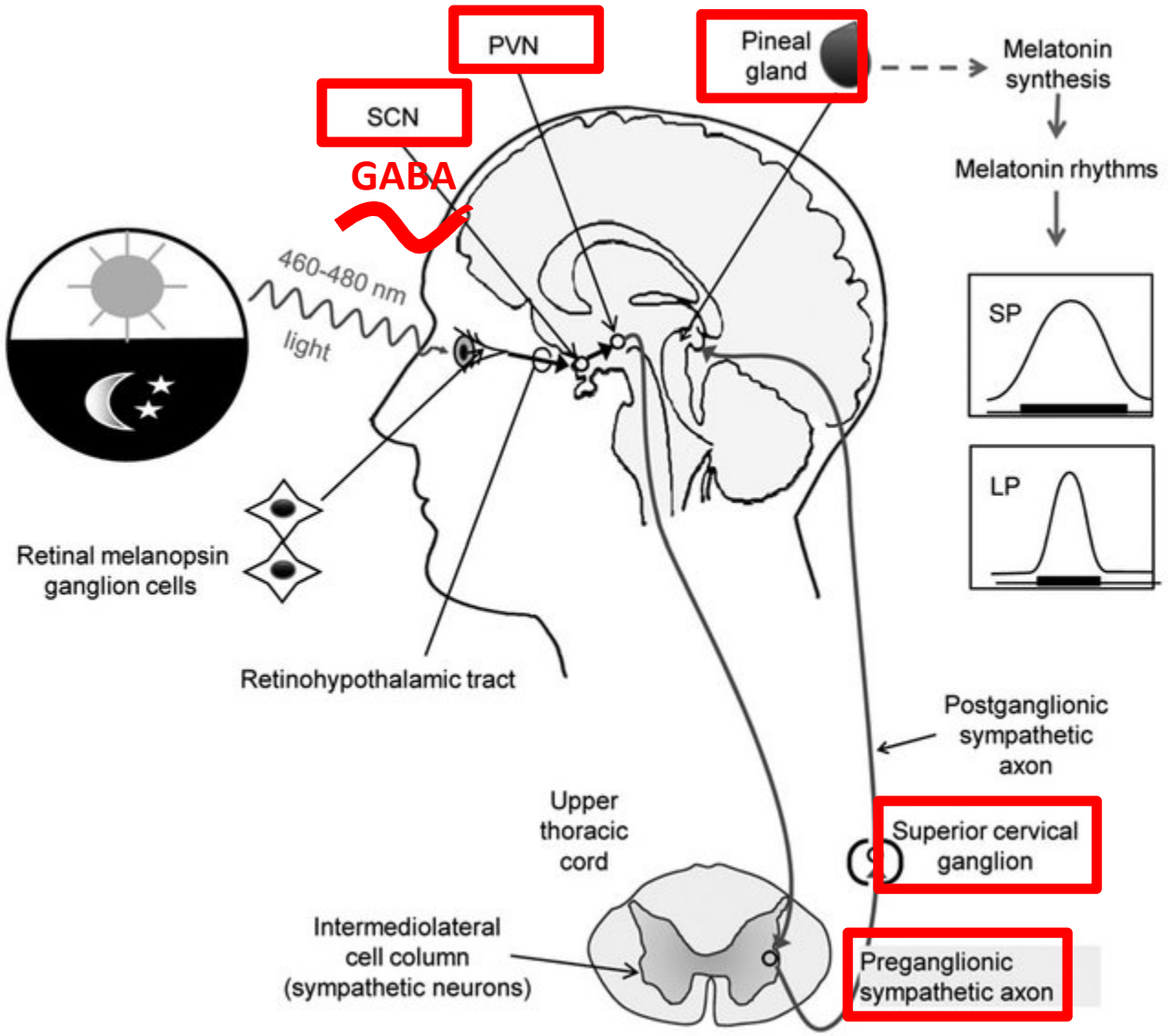
melatonin comes from PVH



Saper et al 2005

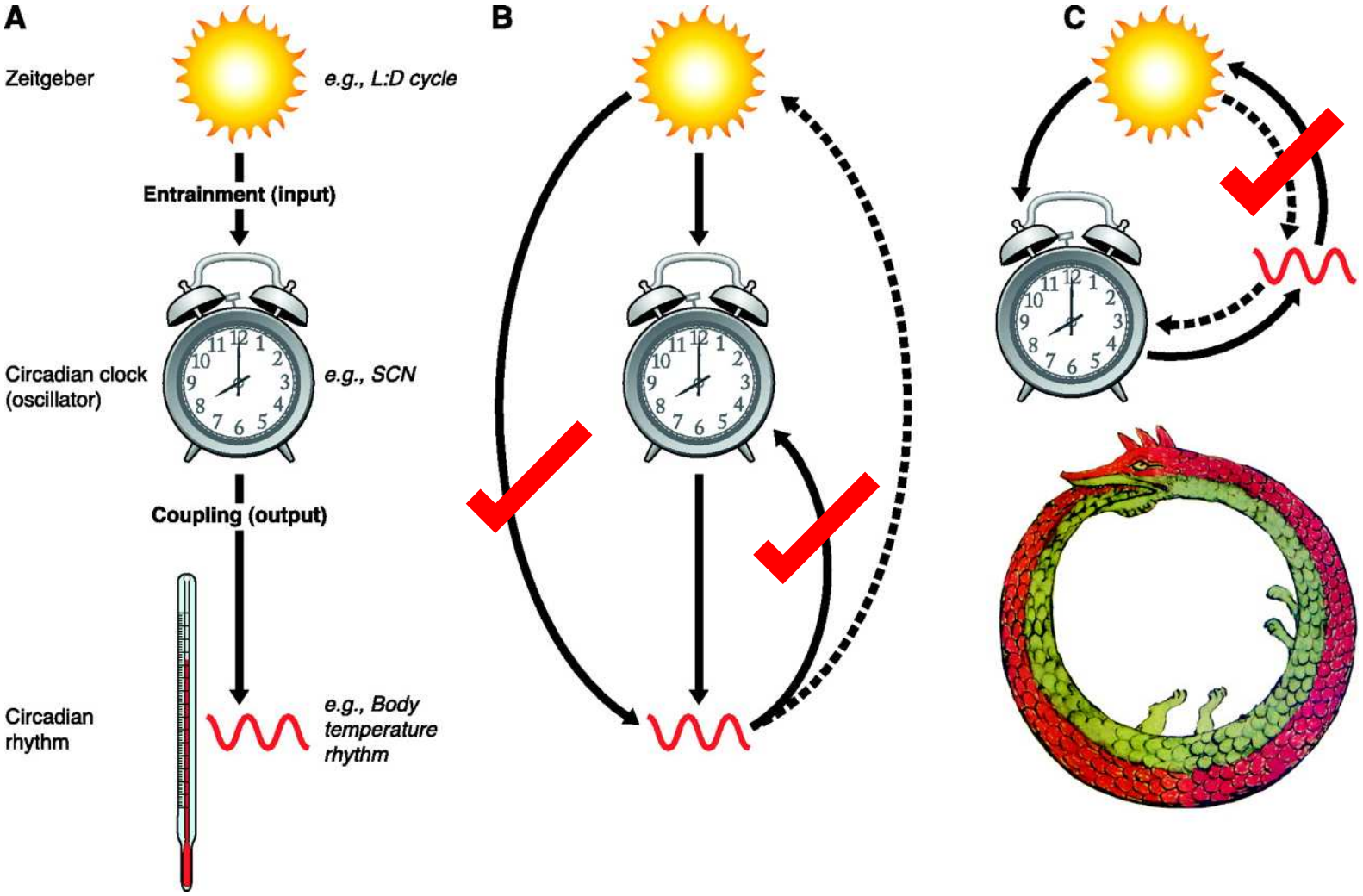
SCN: GABA is nt during the day. PVN is therefore inhibited. in night, GABA release goes down

Pineal Gland: Melatonin Secretion



Tan et al 2010

Circadian Timing is a Function of the Nervous System



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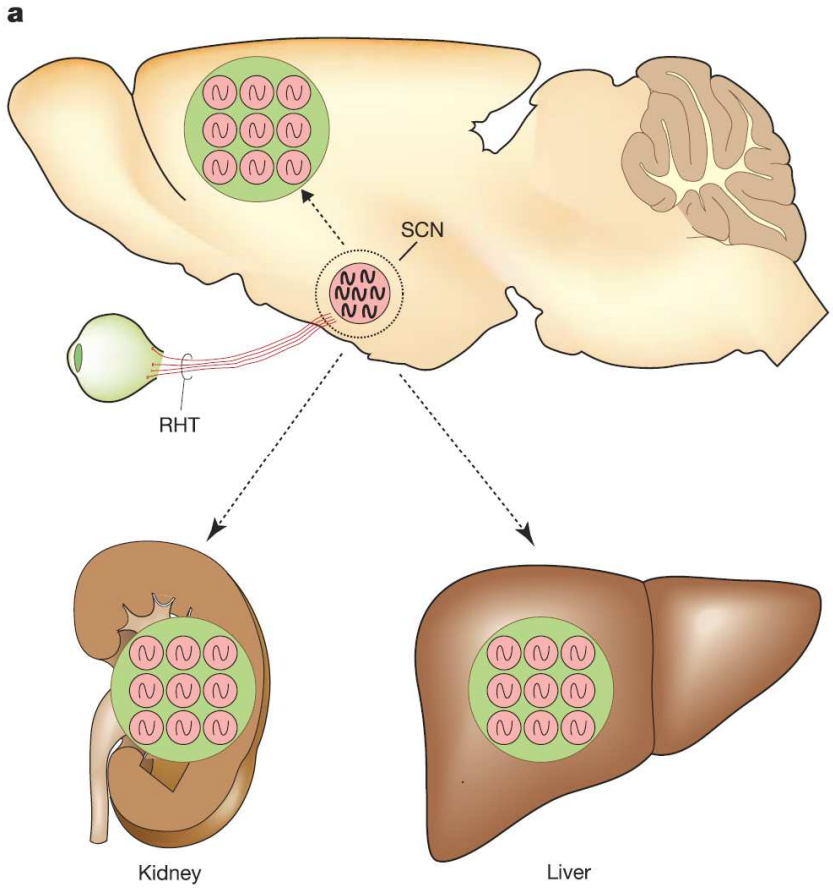
Peripheral Oscillator

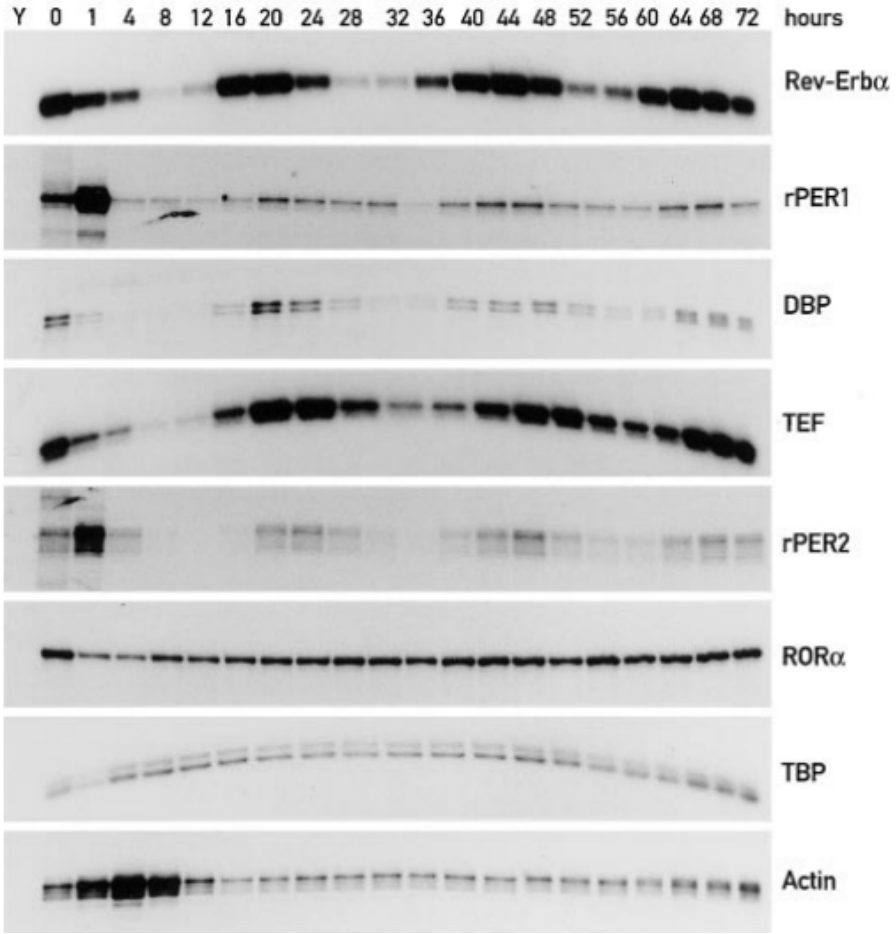


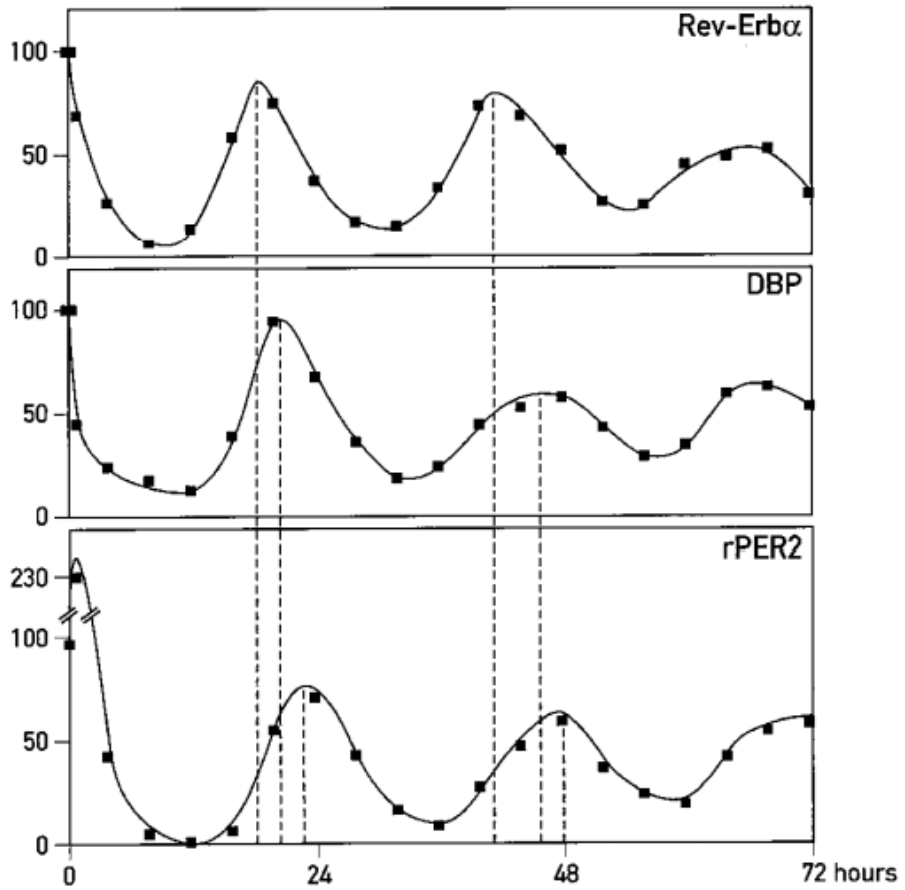
these organs not sensitive to light
but oscillate to different cycles

Reppert&weaver 2002

Peripheral Oscillator

Serum shock leads to cyclic gene expression in fibroblasts

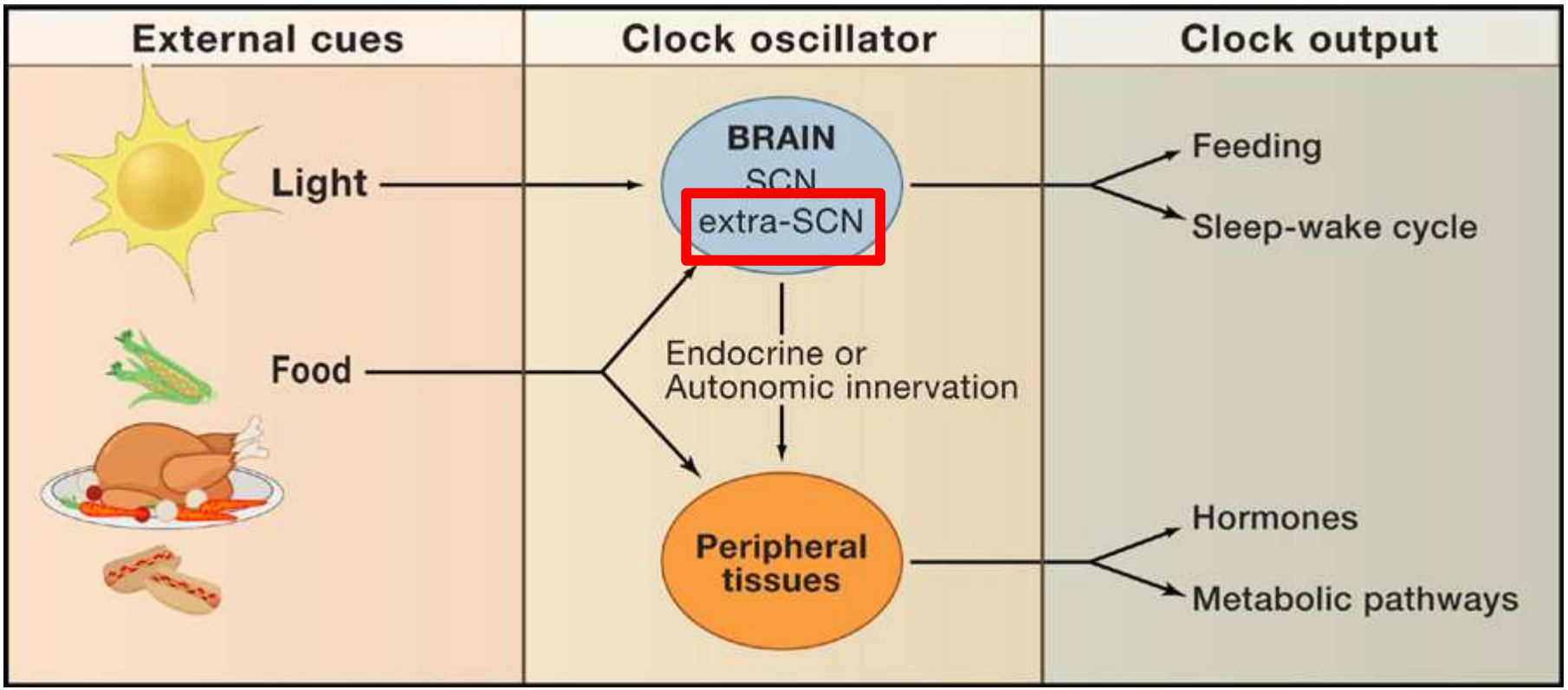




AurélioBalsalobre et al 1998

Food Can Entrain Circadian Clocks

Food-Entrainable Oscillator (FEO)



next to light, food is 2nd most important entrainment object. if mice get food at same time always, they produce anticipatory behaviour after some time.

Carla B. Green et al 2008

for food entrainmeint, central pacemaker is extra-SCN, since mice were still able to become entrained and make food anticipatory behaviour

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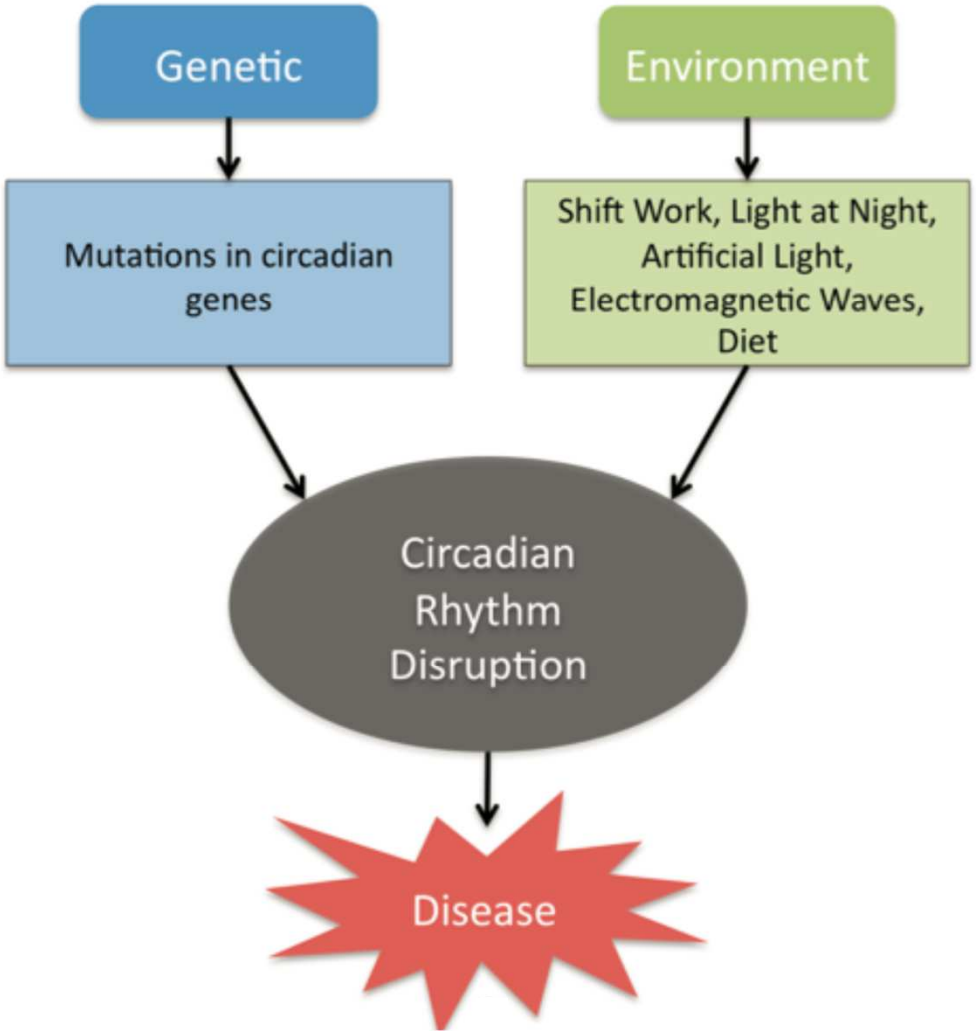
Circadian Clock in Disease: When Time Fails



Rüger and Scheer, 2009

Circadian Clock in Disease: When Time Fails

Sleeping disorders: Familial Advanced Sleep-Phase Syndrome *per2*

Neuropsychiatric disturbances: Seasonal affective disorder

internal clock fails to adapt to winter times

Cancer: Night shift ---------- >>> impaired melatonin

- Breast caner *per3* or possibly all *per* family
- Colon cancer *per1*
- Chronotherapy

Metabolic Diseases : diabetes, obesity *Clock, Bmal1*

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