CIRCADIAN RHYTHM AND ITS DISORDERS

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The scientific discipline studying the biological rhythms and their regulation is called **chronobiology**.

Entire life has adapted to day/night rhythm.

Organisms have developed their own (endogenous) oscillators which show rhythms of approximately 24-hour long periods. These rhythms are called circadian and include circadian rhythms of hormones release, body temperature, sleep/wake cycle, physical activity rhythm and many others.

The primary circadian oscillator (so-called central circadian pacemaker) is located in the suprachiasmatic nuclei (SCN), located above chiasma opticum in the hypothalamus. It is known as mammalian "biological clocks". The circadian pacemaker run with an endogenous period of approximately 24 hours and is denoted by the Greek letter τ (tau). In the humans, the τ (tau) varies across individuals, spanning from 23 to 25 hours (usually more than 24 hours) but is very stable on an individual level. The circadian rhythms are driven by rhythmical expression of the clock genes, leading to rhythmical production of clock proteins. The clock gene expressions fluctuate cyclically due to an existence of an interlocked feedback loops of the gene products (implicated genes: Clock, Bmal 1, Per, Cry; implicated proteins: CLOCK, BMAL 1, PER, CRY). As endogenous period differs from the day/night cycle (i.e. it is slightly longer or shorter than 24 hours), they must be synchronized by external stimuli. The central pacemaker is synchronized particularly by the light. However, food consumption, physical activity and other stimuli also contribute the synchronization.

Light as the main synchronizer of the endogenous circadian rhythms: As the light comes to the retina, it is detected by the layer of ganglion cells. Generally, the ganglion cells process information also from other retinal cells ("classical" photoreceptors rods and cones) and send the information to the brain via their axons constituting optical nerve. However, some of the ganglion cells are directly photosensitive. They are called intrinsically photosensitive retinal ganglion cells (ipRGCs). The ipRGCs contain photo-pigment melanopsin which mediates the synchronization of the circadian rhythms with the environment and constitutes the most upper retinal layer capable to detect even low-intensity light. In contrast, the cells capable to detect visual information (rods and cones) are located in the deeper retinal layer.

Light-induced synchronization in retinohypothalamic tract (RHT):

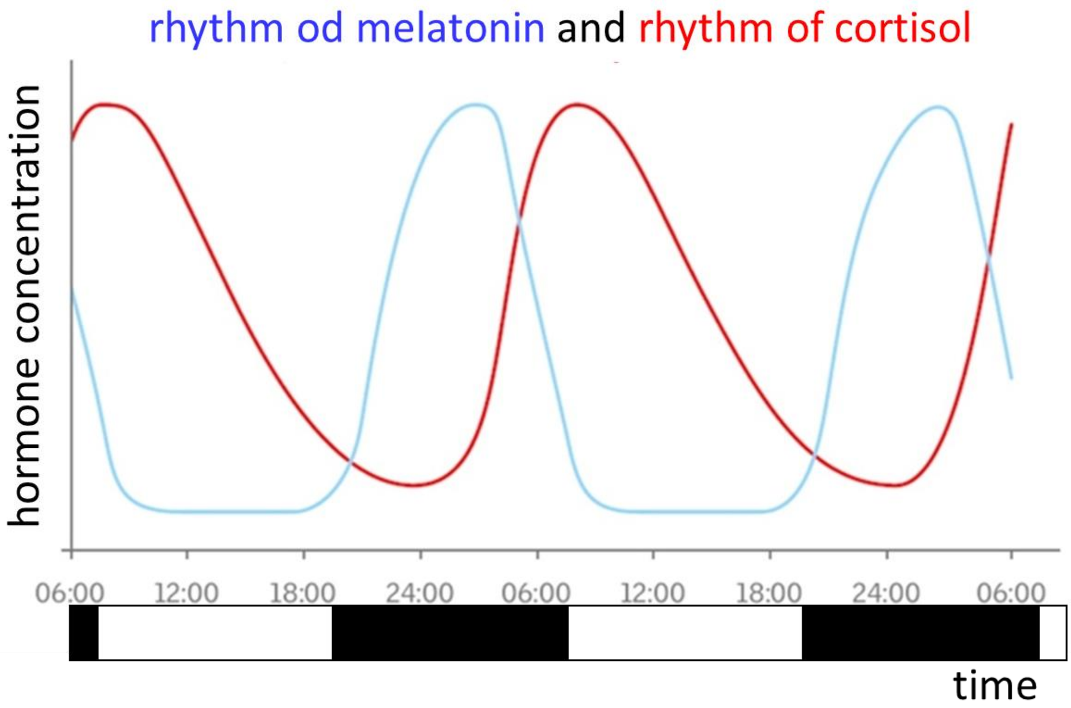
Light → retina → photosensitive ganglion cells (ipRGCs) → glutamate → SCN

The light coming on photosensitive ganglion cells (ipRGCs) activates the photopigment melanopsin. This causes excitation of the cells which further leads, via axons, to suprachiasmatic nuclei. The pathway depends on neurotransmitter glutamate.

Melatonin as synchronizer of endogenous circadian rhythms:

The synchronization of the circadian clocks crucially depends on the melatonin, the hormone produced by epiphysis (pineal gland). The melatonin is produced from amino-acid called tryptophan and is rhythmically released by epiphysis during darkness in the time of subjective night. In opposite, melatonin production is inhibited by light. The rhythmical melatonin release is driven by the SCN. Simultaneously, melatonin release itself affects the circadian clocks in the SCN via a feedback loop, causing an inhibition of the SCN activity. Information concerning light is led to the SCN via the retinohypothalamic tract (see above). Next, the cells in the suprachiasmatic nuclei release inhibitory neurotransmitter GABA. During the darkness, the GABA level drops but the synthesis of the melatonin activates.

The information from the SCN get to the pineal glands via the following pathway: the information from the SCN goes to paraventricular nuclei of the hypothalamus (PVN), further leads via the lateral grey column of the spinal cord into the superior cervical ganglion. The superior cervical ganglion contains sympathetic nerve fibres which release the norepinephrine during the darkness, stimulating the cells of the pineal gland to melatonin production (via ß1 adrenergic receptors). Melatonin shows distinct circadian rhythm accompanied by high melatonin level during the night and almost zero melatonin level during a light period. This rhythm is endogenous and is preserved even in total darkness. As another example of the rhythmical production of hormones, the level of cortisol is very low during the night but high in the early morning time. Other examples: awake/sleep cycle, body temperature oscillations (the highest in the evening, the lowest in the morning), physical activity cycle (high activity in the forenoon and late afternoon but low activity at noon and early afternoon). On a molecular level, expression of genes (and related production of protein) also shows rhythmicity.



A phase of the biological clocks is reflected by the melatonin cycle. Melatonin has several very important functions for the body:

Functions of melatonin:

- Fine-tuning of the circadian pacemaker in the SCN
- Informs the organisms about a day/night length (photoperiod signal)
- Hypnotizes and induces sleep
- Protects the skin from UV light-induced damage
- Protects cells against reactive oxygen species (antioxidant properties) and shows anti-tumour and anti-ageing activity
- Modulates hormone release (especially sex hormones) and thus affects sexual maturation. Inhibits release of prolactin, luteinizing hormone (LH) and follicle-stimulating hormone (FSH).

- Contributes to the modulation of the immune system (melatonin is released also by white body cells).

Pathophysiology of circadian rhythms

The amplitude of the melatonin level fluctuations decrease during ageing. The synchronising effect of biological clocks also decreases during ageing (i.e. “rhythms desynchronization”). The rhythms desynchronization occurs also in response to isolation from external synchronizers. In such a case, the circadian clock runs with endogenous period τ (tau) and the synchrony of various rhythms of the body is broken. For example, the wake/sleep cycle deviates from 24 hours after 2 months spent in the non-periodic environment, whereas body temperature usually follows the 24 hours.

Endogenous desynchronization occurs:

- in persistent darkness

- in blind people with damaged retinal layer and loss of retinal ganglion cells

- under strong light in the night

- in night work shift and after changing day/night work shifts

- after flights crossing time zones (“Jet-lag” symptoms: sleep disturbances, tiredness, nausea, loss of mental concentration)

There are two effects of the light on the biological clocks

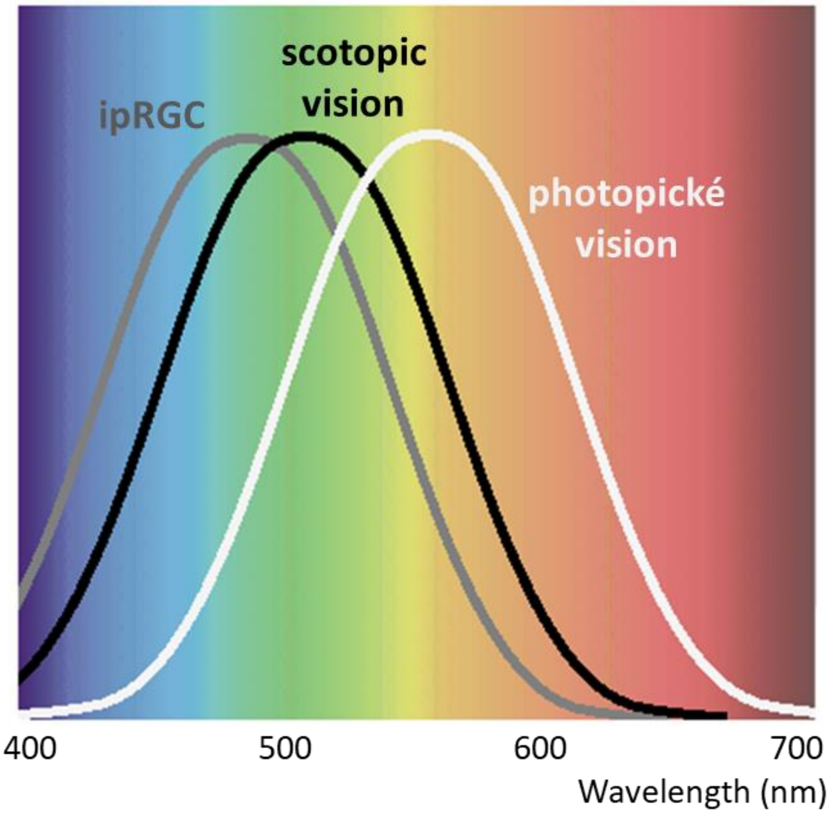
Positive:

The light could be used to synchronize biological clocks. Early-morning light could speed up the circadian pacemaker whereas evening light can delay it. Although sunlight during a day does not cause phases shifts, it is important for strengthening the circadian system. Therefore, lack of exposure to direct sunlight (e.g. due to staying indoors for the whole day) could lead to mental issues and depression.

Negative:

Although daylight has a generally positive effect on health, the opposite is true for the night light. Many health issues may be related to shortening the darkness period. In the darkness, the body synthesizes melatonin and repairs itself at the cellular level. It has been shown that sleeping in an insufficiently dark room could increase the probability of having breast and prostate cancers. The negative impact of exposition to blue light during the night:

The blue light has rapidly spread over the last 20 years due to the massive expansion of LED technology in artificial light, TV, PC and phone screens, consequently leading to disturbances in circadian clock and health. Why is the white light from LED so harmful whereas yellow light from sodium lamp or candles are not? The white light includes a full-colour spectrum, including the blue colour. As you can see on the picture, the photosensitive retinal ganglion cells are sensitive to blue (or blue-green) light. Therefore, the blue light can shift phase of the biological clock in the brain and thus affect our circadian system. In contrast, "warm" yellow light is hardly detectable by the photosensitive retinal ganglion cells and is thus recommended for use in the evening and the night. In case of LED light, the colour temperature must be under 2700 kelvins (the information is shown on covering). The same rules should be applied also for street lights. It is not recommended to use blue light minimally 1 or 2 hours before sleeping. Alternatively, you can use "red glasses" or red filter on screens of phones or PC (lowering of brightness alone is not sufficient). Without these interventions, the synthesis of melatonin is broken, leading to increased risk of various diseases including sleep disorders, hypertension, strokes, cancers, hormone diseases, diabetes (2nd type), obesity, anorexia and abdominal pain.



Spectral sensitivity of individual retinal cells (photopic – cones, scotopic = rods, pRGC – photosensitive retinal ganglion cells). Maximal sensitivity of the pRGC is around 480 mm (blue).

Knowledge of chronobiology could contribute to the solution of many disorders related to the disturbances in circadian clocks. Nowadays, chronobiology represents a highly advanced scientific field with numerous implications for human health and medicine. The research of the molecular basis of the circadian system was even awarded by Nobel Prize for physiology and medicine in 2017.