BIOLOGICAL RHYTHMS

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Summary

Rhythmic behavior is one of the basic concepts of life: all forms of life express some types of rhythms like annual, seasonal, lunar and circadian rhythms. Circadian rhythms affecting everyday life of most species are inborn e.g. in humans, endogenous rhythms that normally are entrained to the solar, 24h period. Endogenous clocks serve to anticipate daily changes in their environment. The manifestations of these clocks are circadian rhythms. They are defined by periodicity in the absence of exogenous cues. The circadian rhythm of mammals originates from the suprachiasmatic nucleus (SCN), a small group of cells in the brain. Recently several genes that participate in the regulation of circadian rhythms have been cloned.

In humans the most important circadian rhythms are sleep-wake cycle, temperature rhythm and the rhythms of several hormones (e.g. melatonin, growth hormone and cortisol). Normally these rhythms are synchronized in a physiologically relevant manner. During shift work the internal rhythm will be uncoupled from the external

light-dark rhythm, which may induce desynchronization of rhythms: a person must sleep during the day time, when the temperature and the cortisol secretion are high, while the melatonin secretion is low. Flying over several time zones will induce a jet lag syndrome—also a state of desynchronization. Symptoms are similar: excessive sleepiness, irritated mood, somatic symptoms (headache, stomach problems) and decreased performance. Chronic exposure to desynchronization of rhythms may increase morbidity.

1. Introduction

Almost all physiological functions express some kind of rhythmicity. The period of the rhythms may vary from very short, ultradian rhythms (with period less than 24 h) e.g. the rhythm of the heartbeat to monthly or annual rhythms of reproduction. Rhythmic behavior is found perhaps in all organisms—as a matter of fact the phenomenon of inborn, daily rhythmicity was first described in plants by de Mairan in a publication from the year 1729. The ability of an organism to anticipate the changes in environment, not just react to them, has evidently offered an evolutionary advantage that has remained through the different phases of the development of life.

The following will concentrate on daily, **circadian rhythms**. The most common outputs of circadian rhythms are sleep/wake cycle, rest activity cycle, body temperature rhythm and circadian rhythmicity in hormone secretion (e.g. growth hormone, cortisol and melatonin).

The circadian system consists of three parts: input pathways to the clock to entrain it, the central oscillator (the clock) and output pathways to generate the behavioral rhythms (e.g. sleep/wake or temperature rhythms).

2. Circadian Rhythms are Endogenous

Circadian rhythms in rats and hamsters can be studied non-invasively by measuring their drinking behavior or motor activity either by a running wheel or using an infrared beam to record their movements in the home cage. Under normal lighting conditions (e.g. 12h dark, 12 h light) the motor activity starts exactly at the same time of the day, one day after another. Under these conditions the motor activity is tightly **entrained** to the 24 h period of the environment.

If the animals are moved to constant darkness, the rhythm of the motor activity remains periodic, but the timing of the start of the motor activity is shifted every day to either a slightly later or earlier time point, depending on the species. Animals that cannot convey light information from retina to the brain behave similarly.

Thus if the external light cue is lacking, or the animal cannot respond to it, the animal behaves according to its internal rhythm, that has a slightly different period than the solar 24 h period. This unentrained rhythm is called a **free running rhythm**. This applies also to human beings, as evidenced by several experiments where human volunteers have stayed under conditions where they receive no time cues from their surroundings.

3. Entrainment

When organisms were maintained in constant darkness, it was found that a single pulse of light could advance, delay or have no effect on the rhythm, depending on the time of the exposure to light in relation to the endogenous oscillation.

The internal rhythm will be entrained to environment daily by a zeitgeber, which literally means "the giver of the time". The most important zeitgeber is light. The light signal is received in the retina, and is then moved forward to the SCN through the retino-hypothalamic pathway. This pathway runs parallel with the optic nerve, but its target is the suprachiasmatic nucleus in the hypothalamus and it possibly uses a non-classical photopigment, namely melanopsin which is expressed in a subset of PACAP-containing retinal ganglion cells, to convey the circadian light response. Another, indirect pathway runs from the retina to the lateral geniculate nucleus (LGN), and from LGN to the SCN (see Figure 1). The phase of the internal rhythm can be shifted with a pulse of light.
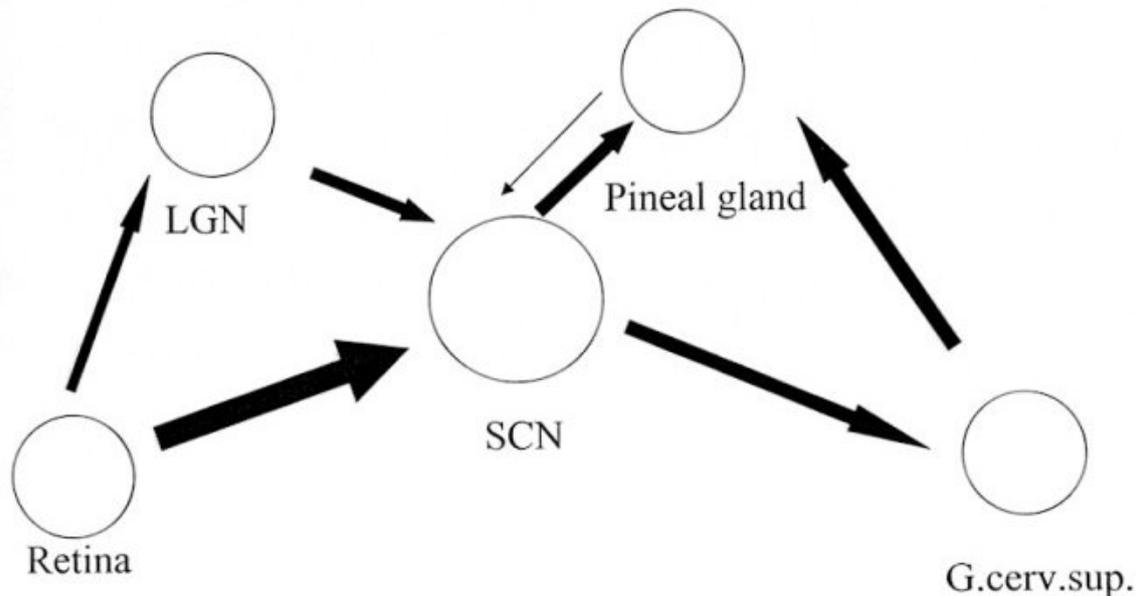

Figure 1. Anatomy of the time keeping system.
The retina receives light information that is used for entrainment. From the retina the information is distributed through three different pathways to the central nervous system. The main pathway targets the suprachiasmatic nucleus (SCN) (the retinohypothalamic pathway). Another pathway will target the lateral geniculate nucleus (LGN), which sends the information further to the SCN. The third light information pathway targets the pineal gland, through an indirect pathway that enters via an autonomous ganglion, ganglion cervicale superior (G.cerv. sup.). SCN entrains the rhythm of melatonin secretion from the pineal gland, but it is possible that also the pineal gland participates in the entrainment of the circadian rhythms by affecting the SCN.

The timing of light pulses is of crucial importance. If the light pulse is given in the middle of the day or in the middle of the night it has very little effect on the rhythm. When given either during dawn or dusk, the internal clock can be reset by an hour or

more, depending of the brightness of the pulse. A phase-response curve describes the relationship between the timing of the light pulse and the amount of resetting of the internal rhythm (Figure 2). The magnitude of shifting is dependent also on the amount of light (illumination)―in rodents very small amounts of light are sufficient (1-5 lx), but in humans typically at least 200 lx are required, usually 1000 to 3000 lx are necessary. The ability of light to entrain circadian rhythms decreases with aging.

Light is the most important, but not the only entrainment signal to the SCN. Feeding time and other social cues as well as motor activity (possibly through a serotonergic input to the SCN) can also entrain circadian rhythms.
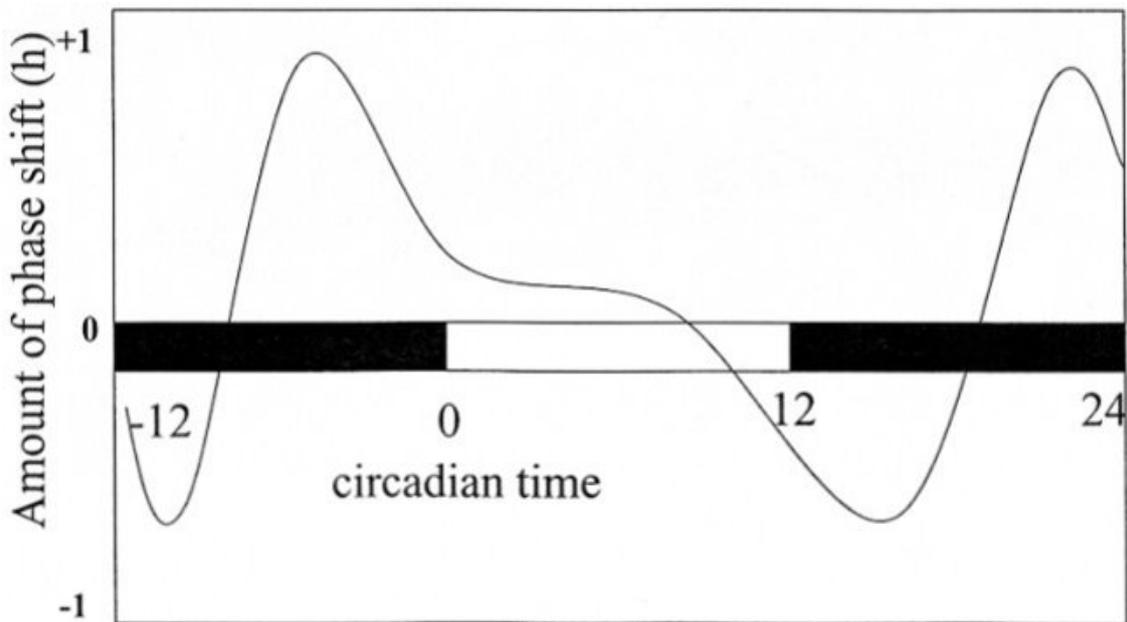

Figure 2. The phase response curve (PRC).
Entrainment by light is not equally effective at all time times of the day. The phase response curve describes the amount of entrainment, which can be obtained through the day. Entrainment is most effective at dawn and dusk, and least effective at noon. The entrainment can either advance the rhythm (positive deviation) or delay it (negative deviation). Dark bar = subjective night, clear bar = subjective day. It should be noted that the details of the phase response curve are variable in different species and with different zeitgebers.

4. Rhythms in Plants

Circadian rhythms were first described in plants as early as 1729―the movement of leaves (in *Mimosa pudica*) was shown to be intrinsic, not solely regulated by the light/dark cycle. The rhythmic events in plants are not restricted to leaf movements. Growth, (cell elongation) stomatal aperture, hormone production, Ca^{2+} concentration and expression of many genes also exhibit circadian rhythm.

The rhythm in plants can be phase shifted, as in animals, by light, but temperature also acts as a strong resetting stimulus. In plants several rhythms with different periods run simultaneously (internal desynchronization). Thus the plants do not have a systemic phototransduction signal that coordinates the plant circadian system, like the SCN signal

in animals. The genetics of the plant circadian clock has been studied in *Arabidopsis thaliana*.

5. Rhythms in Animals

The expression of rhythmic behaviors is not restricted to mammals—even the simplest forms of life, including unicellular organisms, express rhythmic behaviors. According to the timing of the activity period, animals are divided into two categories—if they are active during day, they are **diurnal**, if active during night, they are **nocturnal**. One of the reasons for this diversity is obviously the increased opportunity for several species to inhabit the globe; more ecological departments are available, when animals "work in two shifts".

Most of the research on circadian rhythms is performed on one of the following species: cyanobacteria (*Synechococcus*), fungi (*Neurospora crassa*), insects (fruit fly *Drosophila melanogaster*), and for the vertebrates the golden hamster (*Mesocricetus auratus*) and the mouse (*Mus musculus*, especially for genetic research). The genetic organization of the circadian system in different species appears to be rather similar; gene homologies are common.

6. Suprachiasmatic Nucleus (SCN)

The SCN is a paired group of brain cells (about 20 000) that in mammals lie in the ventral part of the hypothalamus, above the optic chiasma. It is composed of two anatomically and functionally distinct subdivisions, the core and the shell, which can be distinguished both anatomically and according to their connections. Most SCN neurons produce GABA, which is co-localized with peptide neurotransmitters (e.g. VIP and GRP) (see *Neurotransmitters and Modulators*). The core is the ventral part of the nucleus that lies closely to the optic chiasm. It contains vasoactive intestinal peptide (VIP) and gastrin releasing peptide (GRP) -containing neurons. The core receives direct visual input from the retina and secondary visual input from the intergeniculate leaflet (IGL) (See Figure 1). The shell contains arginine vasopressin (AVP) containing neurons, and receives input from limbic, hypothalamic and brainstem nuclei. Early SCN lesions, which in mammals abolished the circadian rhythm, led to the conclusion that SCN is the key pacemaker of the body. Conclusive evidence was presented, when SCN transplant from a mutant animal (tau mutant in hamsters, with a period of 20 h) was operated to an SCN-lesioned animal, which after the operation started to express the rhythm of the mutant hamster. Transplants from normal hamsters created circadian rhythms with normal periods.

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Biographical Sketches

Tarja Porkka-Heiskanen is presently working as a senior researcher at the Academy of Finland. She defended her dissertation in 1990 at the Medical Faculty, University of Helsinki. She did her post doctoral research at the Northwestern University, Chicago, IL with Professor Fred Turek, and returned to the Department of Physiology, University of Helsinki. A later two-year research period in the USA was done at Harvard Medical School as associate professor with Professor Robert W. McCarley. She is interested in the mechanisms of sleep, particularly the regulation of rebound sleep after prolonged wakefulness. She has also done research on circadian and annual rhythms, and neuroendocrinology. She has published more than 80 original articles (among others in Science, Endocrinology, Journal of Neuroscience) and several reviews.

Jarmo T. Laitinen presently works as a senior research associate at the Department of Physiology, University of Kuopio. His PhD thesis (1983) dealt with seasonal rhythmicity in the conception and lactation of dairy cows. He did his postdoctoral studies as a visiting fellow at the National Institute of Mental Health, Bethesda MD, under the supervision of Dr. Juan M. Saavedra with major emphasis on the identification and characterization of melatonin receptors with receptor autoradiography. Dr. Laitinen's current research deals with G protein coupled receptors. He has published about 50 original articles in international peer-reviewed journals, such as Journal of Neurochemistry, Neuroscience, Endocrinology, and PNAS.