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Light, circadian and circannual rhythms

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Abstract

Organisms use circadian and circannual rhythms in cells or cell complexes for time measurements, thus the term biological clocks. Properties and models of biological clocks are discussed. In mammals, the biological clock system perceives light signals via the retina. Signals are then led to the suprachiasmatic nucleus (SCN) of the brain, functioning as the central clock region. Via pathways – involving the pineal organ and its production of the ‘sleep’ hormone melatonin – the rhythmic signals from the SCN affect body cells, hormone balances etc. Light strongly affects the circadian rhythms and also circannual and seasonal phenomena. Light can trigger the SCN and cause phase shifts of the circadian rhythms. The rhythms can be used by organisms to measure day/night length and control processes that should start at specific times of the year (photoperiodic control). Health effects might be expected when the clock system has deficiencies. Clinical effects of malfunctioning circadian light perception and of defect functions of the circadian system are discussed. Rhythm disturbances can result, for example, in sleep disorders and in depressive syndromes, and are connected with forms of cancer etc. Therapeutic effects of light treatment are reported. So-called Seasonal Affective Disorders (SAD) are reported to be light dependent and light treatment successful in several cases. Light induced rhythm disturbances also occur due to shift-work or jet travels over time zones.

Introduction

Many physiological processes in organisms occur in a *daily* fashion. This is true also for man. Light can provoke such daily changes via the sun dependent *external* light-darkness variations. However, also under constant environmental conditions many physiological functions appear in a daily fashion. They are then

generated by *internal* rhythms, which can be studied in isolated units, free from external variations. Such conditions can be found in bunkers, caves, suitable laboratories etc. The rhythms then show a period close to 24 h – but not exactly 24 h. They are termed *circadian* rhythms. The word emanates from Latin *circa* + *dies* (day). They are found in almost all living beings, from prokaryotes to higher organisms. In a corresponding manner physiological events can be regulated by external, yearly or seasonal variations or generated by internal mechanisms that have a period of about a year, *circannual* rhythms. Such rhythms are found in plants, animals, and man.

It may seem easy to distinguish between externally and internally regulated rhythms. In fact, it can be very difficult. However, if the organism is isolated and deprived of all external signals – including the daylight variations – that can provide time information and the physiological rhythm then shows a period deviating from 24 h one can draw the conclusion that the rhythm is internally controlled. One can then speak of a proper circadian rhythm. Correspondingly, a true circannual rhythm should have a period close to but not exactly one year (under constant conditions). Under normal environmental conditions the internal rhythms of the organisms *adapt* their period to the light regime of the sun and, therefore, show a daily 24 h rhythm.

The following pages will mainly focus on some aspects of human circadian rhythms and their intimate relation to the external light conditions. The relation between the human rhythms and health will be a basic topic. However, examples of rhythms and mechanisms found in other organisms will be discussed as well.

The circadian rhythms – “biological clocks”

Some features seem to be shared among circadian rhythms in most organisms. They

- have a period of roughly 24 h (about 18 and 28 h in extreme cases) under constant external conditions
- have a period that is only slightly dependent on temperature (if constant)
- function on the cellular level and are heritable
- are sensitive to lithium ions which lengthen the period in many organisms
- can be *phase-shifted* by light or dark pulses. They can thus adapt to light/darkness schemes as provided by variations in light intensity. (One often says that the rhythms are *entrainable*, or possible to entrain to the light scheme.)

The action of light will be in focus in this paper and it is proper to emphasize the last point above: most circadian rhythms can be “set” (‘phase shifted’) by light

pulses. So if a jet plane passenger arrives at a new time zone the rhythm can be adapted to the new light program. The property of light pulses to phase-shift the rhythms is intimately connected with clocks' ability to adapt to the environmental 24 h light program – the exact 24 h day/night change – even if their internal period deviates from exactly 24 h. The circadian rhythm can be used to provide information about time to the organism, i.e. they can be used as *biological clocks*. As such they are also used to organize temporally physiological processes in the organism. Light plays the role of a very effective signal for the biological clocks and its adjustment to the external 24 h conditions. However, the adjustment takes time and when the circadian rhythms are abruptly out of phase with the solar rhythm, several days are needed to come into phase again (typical in 'jet lag' disturbances).

Precise period of human clock

The period of the human circadian rhythm has been the object of study for many years. The average period in many such studies under constant conditions has been estimated to be about 25 h (1). Obviously, a circadian rhythm with period equal to 25 h would have to shorten it by 1 h every day to adapt to the 24 h external period. However, recent experiments have shown that this might be an overestimate of the natural period (found if the organism was kept in 'constant darkness'). Using special experimental protocols the period could be measured without the influence of self-selected sleep/wake and light/darkness cycles (2, 3). It turned out to be much closer to 24 h, one value reported is 24.2 h on the average (core temperature rhythm; independent of age and gender of subjects). To adapt the circadian clock of a person with such a period to the external exact 24 h day, the rhythm has in principle to be advanced daily only by about 12 minutes. The circadian period of the human biological clock is *less* than 24 h in about 25% of persons tested.

- The period of normal human subjects adapts to exactly 24 h under the influence of the normal light/dark conditions.
- The period depends on the light program and light level!
- The period can be extreme, e.g., for sleep/activity rhythm (an example: recordings of 46 h rhythms are reported).

Figure 1 exemplifies the core temperature rhythm of a subject under fairly constant conditions (4). Conditions were summer time in Svalbard (about 70 °N) with almost constant light and temperature throughout day and night (and of course without watches, radio, regular contacts etc.). The sampled body temperature shows a marked minimum in the subjective night, rhythmic features during sleep and irregularities during subjective day with physical activity etc.

The period clearly exceeds 24 h as estimated from the temperature minima and the person is 'free-running' (not adapted to 24 h).

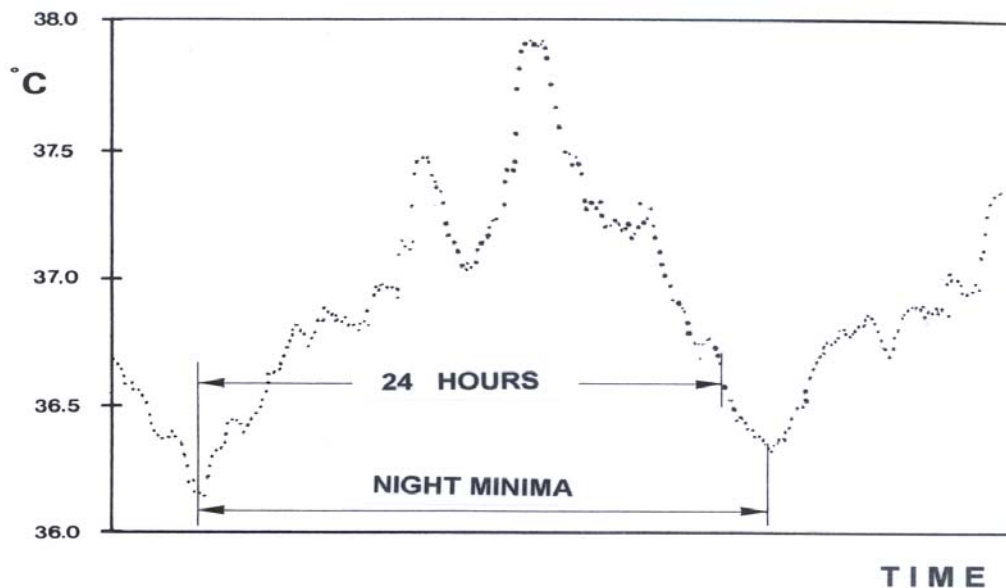


Figure 1. Temperature recording of circadian rhythm.

Core temperature was continuously sampled from a subject living under summer time conditions in Svalbard. Environmental inputs are then almost constant and the human biological clock shows its natural period ('free-runs').

Night minima are more than 24 h apart, as indicated. Temperature variations with shorter periods (during parts of sleep) as well as activity induced temperature peaks are discerned.

Circannual rhythms

In accordance with the definition of circannual rhythms one must look for rhythms that have a period that is *about* a year when unperturbed by environmental signals. Again, seasonal influences from the environment might mask the circannual rhythms in a way corresponding to the daily influences on the circadian rhythms. However, regular light/darkness signals can be given to organisms and their activity pattern studied in long term experiments over several years. Results from such experiments are exemplified in fig. 2, where gonad size and moulting of starlings are plotted as a function of time. It is seen that the patterns have a period of about a year.

The seasonal onset of hibernation of many animals and the seasonally determined flowering time of plants are examples of yearly rhythms that are observed in nature. The timing of the onset of such events is often regulated by the day/night length, the *photoperiod*. Also temperature might play a role but usually constitutes a much less precise signal than the photoperiod and does,

therefore, not determine the precise time of the year to start the processes. Erwin Bünning (5) was the first to demonstrate that the circadian rhythms are used as clocks to determine the photoperiod. Experiments corresponding to circadian experiments can be done on circannual rhythms (6, 7). Germination patterns of dry seeds have been studied and show a circannual pattern. Hibernation, eclosion of insects etc. can likewise be shown to appear in rhythmically controlled ways.

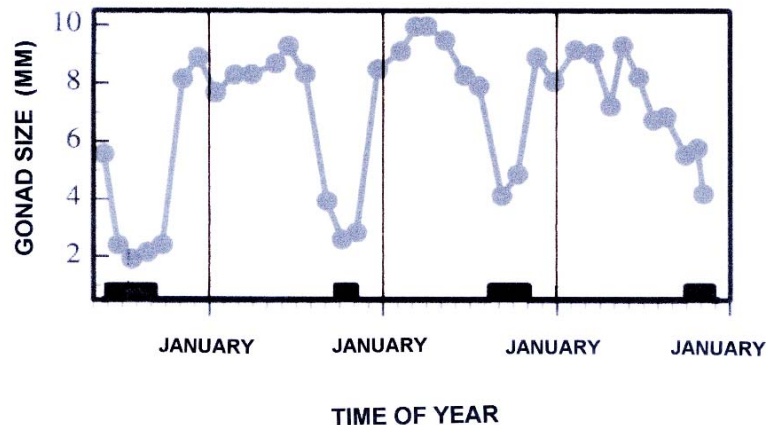


Figure 2. Circannual rhythms – example.

The gonad size (curve) and moult (bars) in starling vary with a period that is close to a year when isolated from external seasonal time cues (adapted after (7)).

Biological clock mechanisms. Light influences

The mechanisms of the biological clocks are intensely studied and are rapidly unveiled. Molecular genetics is currently extremely fruitful in studies of circadian rhythms. In many models of the biological clock, a central element is a *transcription* of clock genes followed by a *translation* and production of central proteins that later inhibits the transcription – the overall reaction being a transcription-translation controlled rhythm or oscillation (a ‘TTO-model’).

One general feature of such proposed clock mechanisms in cyanobacteria, plants, fungi, insects, mammals etc is the *feedback* concept (8). Crucial molecules are rhythmically changing their concentrations in such a manner that when concentration is increased, a negative feedback regulates the production of the same molecule. As a result the concentration decreases until the feedback chain again starts producing the molecule. A totally different clock model has been suggested for cyanobacteria (9, 10). Here the feedback has been found to be based on phosphorylation reactions of a central protein KaiC, which changes

its conformation and bindings in a daily fashion, also in a test tube. No transcription-translation is included in the central oscillator. The rhythms can be circadian, provided that energy and suitable substance concentrations are present; furthermore the rhythm is relatively temperature independent (11). Thus, one has “created” an artificial biological clock in a purely physico-chemical environment, a clock experimentally found in the (unicellular) cyanobacteria *Synechococcus*.

Since light and light programs – mainly the sun light variations – regulate the phase shifting of the biological clocks and the period of the clocks, light also influences the processes *regulated* by the clocks. The *pigment* system that perceives the relevant wavelengths as well as the subsequent signal transport to the central clock vary enormously from species to species, from plants to animals etc. In order to find out which wavelengths are effective in shifting the phase of the circadian rhythms in man, action spectra were determined by using the suppression of the hormone plasma melatonin (see section 6). The results of those and other experiments are compiled and discussed by Brainard and Hanifin (12). Light in the short wavelength range (459 to 484 nm) is most effective. This differs from the spectral sensitivity of the visual system and points to a specialized circadian photoreceptive system. An overview of the biological clocks and their resetting by light is given in (8).

Physiological clock mechanisms in man

Only a very simplified overview of the human clock system can be given here. The central, rhythmic cells in the human biological clock are *localised in the suprachiasmatic nucleus*, the SCN, in the brain. In its basic function the SCN mechanisms resemble those of other mammals. The SCN and its incoming and outgoing pathways are schematically depicted in Fig. 3. The light is perceived via special retinal cells, intrinsically photosensitive retinal ganglion cells, ipRGC, and signals are then fed via the retino-hypothalamic tract (RHT) to the SCN. Light is thus affecting the rhythmic cells in the SCN, from which the clock functions are governed. Of special importance in the subsequent pathways is the one from the SCN (via a complicated loop) to the *pineal* organ. The pineal produces *melatonin*, often called a ‘sleep’ hormone (see inset in Fig. 3). It reaches the blood vessels (emphasized by the arrow in the inset), and thus the blood system of the brain and the body. This allows the SCN to act as a kind of master clock and to synchronize organs, tissues and cells in the body.

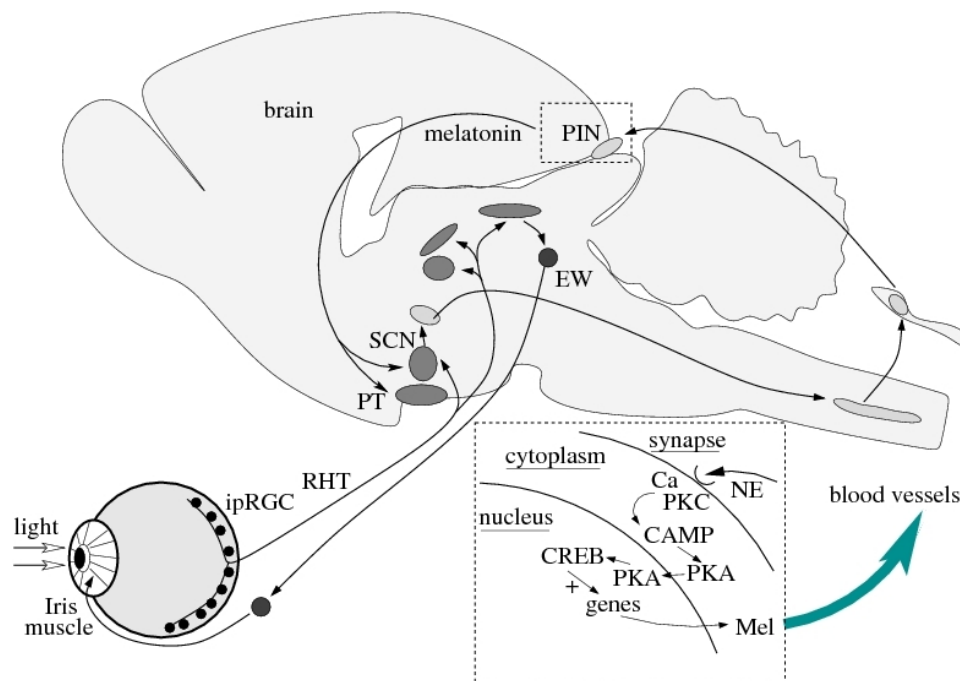


Figure 3. Circadian centres and pathways in mammals.

Light is perceived in ipRGC cells of the retina (intrinsically photosensitive Retinal Ganglion Cells). Signals from them arrive at the suprachiasmatic nucleus, SCN, the main biological clock in mammals. SCN couples – by sympathetic innervation - to the pineal, PIN, depicted in the main figure and in the inset. Melatonin is produced in the pineal, enters the blood stream and affects both the SCN and PT (pars tuberalis, center for photoperiodic control). The melatonin production in the pinealocytes, see inset, takes part via norepinephrine (NE), signalling. The signal cascade involves calcium ions and PKC (protein kinase C), increasing cyclic AMP. PKA (protein kinase A) phosphorylates CREB (transcription factor to bind DNA) in the nucleus, activating gene regulated melatonin production. Melatonin reaches the blood vessels. A special pathway from retina via the EW (Edinger-Westphal) area actuates the papillary light reflex and the iris muscle.

It should be understood that also other circadian centres and oscillators exist in the body; self-sustained oscillations are found in individual organs and cells. The overall circadian system of man is thus a complicated structure where the SCN has been described as a “conductor of the circadian orchestra”. Usually the different organs and functions are synchronized and show a period close to 24 h, as discussed above. The rest/activity rhythm is also normally coupled to the system, but can deviate from the overall rhythm under special conditions or in individual subjects. The period of this rhythm might then deviate substantially from that of the core temperature rhythms.

Since the body temperature, the sleep/wake cycle (13), the amount of urine produced and its composition, the blood hormones etc, can be monitored fairly

easily, they have often been used as ‘hands’ of the circadian system. The melatonin concentration in the blood is a particularly useful measure of the circadian rhythms system since it is not much disturbed by body activities. The action of light on the melatonin concentration is mediated via an effect on the production of the melatonin. A suppression of it starts immediately after signals are given to the pineal while the action on other rhythms like the body temperature rhythm can be considerably delayed. The rhythmic concentration changes of melatonin is thus of great importance in the organization of the circadian rhythms in man. It can be taken up orally and thus be used for affecting the phase of the human biological clock. This can be important in resetting the clock after jet lags or phasing of the clock for example in sleep perturbations.

Light perception by the human body

It has been speculated that light may be perceived also via extra-retinal pathways, i.e. outside the perception in the eye (cf. Fig. 3). In particular it would be important to know if light could act on the rhythms via the skin – for example reaching the blood vessels. The solar irradiation would then be in the position to affect the biological clocks both via the skin (supposedly mostly by red light action since those wavelengths would penetrate better than short wavelengths) and via the ipRGCs.

The penetration depth of light in the skin depends on the absorption and scattering of the different wavelengths. Red light penetrates typically a few millimetres into the skin (a depth at which the intensity has been reduced to about 30% of the surface intensity), blue light is heavily scattered and is reduced by about 30% already at some tens of a millimetre. A report by Campbell and Murphy (14) claimed that it was possible to phase shift the biological clock by light stimulation via the skin. However, this experiment has not been possible to reproduce and it is now a general opinion that all light signals reaching the biological clocks come via the retina (15, with further references). The chromophore molecules in the human retina that are signalling to the SCN are not situated in the ordinary rods and cones. The special circadian photoreceptor cells (distributed in the retina) contain chromophores that absorb light mainly in the wavelength region of 460-480 nm. The chemical nature of the chromophore(s) is still under discussion (see e.g. 11).

Circadian rhythms and light – some clinical aspects. Abnormalities in light perception

As mentioned, light represents a most powerful external signal to the circadian rhythms. Possible defects in the light signalling pathways to the circadian rhythms of the body can be detrimental and lead to dysfunctions in the overall clock system. This in turn can lead to health effects. A very simplified block diagram, Fig. 4, shows blocks, possible to connect with clinical aspects of circadian rhythms (cf. (16)). Cells in the retina receive the light, SCN is activated and interacts with the pineal gland and other oscillatory tissues and cells in the body and controls, via the pineal gland, the amplitude and phase of the melatonin rhythm. A regular light/darkness change in the surroundings causes a (likewise regular) change in the rhythmic events of the body. Dysfunctions in the rhythms can lead to different problems, some of them mentioned in the following blocks of the figure. Finally, the skin as a tissue has also rhythmic functions controlled via the clock – simultaneously it receives light *directly* from the surroundings.

Starting with the light perception, one finds that rhythm abnormalities are ubiquitous among totally blind subjects (17). All humans with bilateral enucleation and 20% of the remaining blind people exhibit free-running circadian rhythms ('blind freerunners', 18). The period seems then to be lengthened by about 3-4% compared to healthy subjects (16). In blind people which are not free-running, the blindness affects only normal vision of images, but not the *circadian* vision based on the intrinsically photosensitive retinal ganglion cells (ipRGCs), or other time cues are used for synchronization (19). Occasionally a free-run is also observed in people with intact vision, although they live in a normal environmental situation (20, 21). It is not known why light (and other time cues) are ineffective in these people. Melatonin can be given to free-running blind people to restore and adapt circadian rhythms (22).

Abnormalities in oscillatory functioning

The oscillatory system can be malfunctioning due to gene mutations in the clock system proper (see circle in Fig. 4). During the last years a number of different gene mutations have been associated with abnormal cell behaviour and only a few fields of interest can be mentioned here.

- Gene mutations in clock systems associated with *increased cancer risks* (due to irregularities in the control of the cell cycle?)
- Polymorphism in the clock gene *per3* linked with *early breast cancer* in young women (23)
- Abnormalities in clock genes *per1*, *per2* and *per3* linked with *gene regulation in tumors, but not in normal cells*

- Clock gene *per 2* mutation associated with *glutamate transporter irregularities* (24)
- Mutation in NPAS2 (paralog of the transcription factor CLOCK) associated with *changes in sleep pattern, locomotor activity, response to feeding cues* etc (25)
- Dampening of amplitude of circadian rhythms may cause clinical symptoms

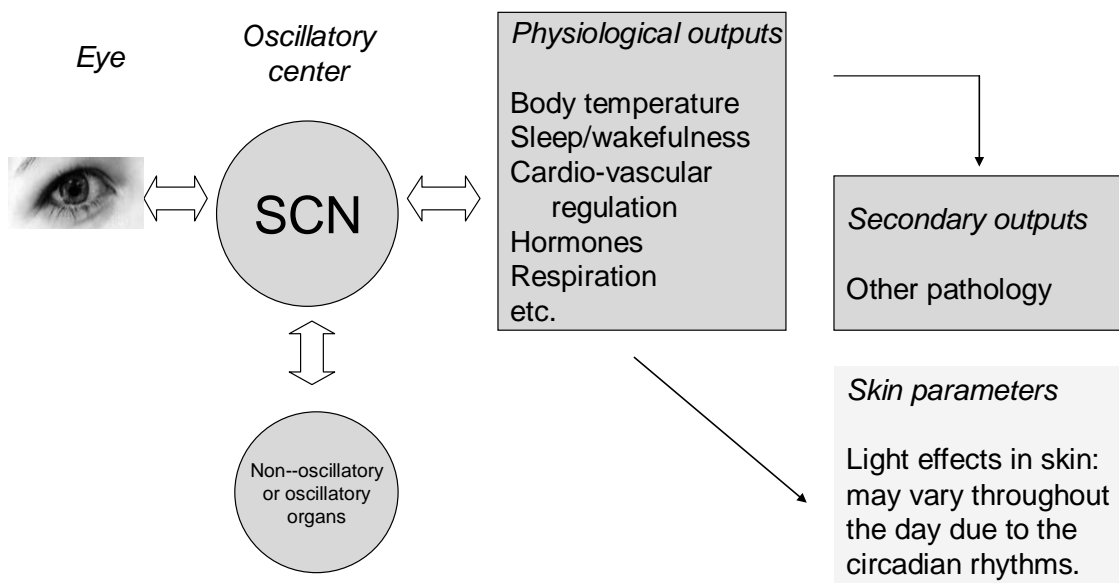


Figure 4. Light, circadian rhythms and possible clinical effects.

Some crucial points where deficiencies in systems controlled by the light and biological clock(s) in man can lead to health effects:

- Light might not be properly perceived in the retina of the eye - left of figure.
- Biological clock cells in SCN (or SCN regulated oscillations) might be deficient or unable to receive or transfer light induced signals – circle symbols.
- SCN exerts control over many important body functions which might be destroyed or badly affected - first block symbol.
- Affected body rhythms can lead to secondary physiological effects – second block symbol.
- Light affects the skin directly, which might cause health problem, but exerts also a circadian control of the skin tissue – lowermost block symbol to the right.

Abnormalities in clock associated physiological rhythms

The first block in Fig. 4, lists some areas in which the circadian clock regulation is participating: variations in core body temperature, in sleep/wakefulness, in many hormone concentrations of the body, in cardio-vascular regulation, in respiratory regulation etc. Only a few specific examples will be mentioned here. In *manic depressive* disorders (bipolar depression), the rhythmic physiological patterns are often perturbed. An example is shown in Fig. 5, where the timing of the daily temperature maximum of a manic-depressive patient is plotted for consecutive days during a time span of several months (26). Furthermore, the mood of the patient is rated (in a scale of black, grey and white to the left). The figure demonstrates that in difficult periods (black) the timing of the core temperature maximum is unstable, while it shows a normal stability throughout period of good mood. Thus, the rhythmic pattern of the patient is perturbed in the depression periods.

We have pointed out that lithium ions have been found to affect circadian rhythms. It lengthens the circadian period in many organisms (27, 28). It increases the period length of subjects living under free-run conditions in Svalbard (29, 4, cf. Fig. 1) (as well as in primates (30)). Lithium was given for some weeks alternating with placebo and the analysis of the rhythms revealed a period lengthening in this case of about 1.2 h. Interestingly, lithium is a remedy against manic-depressive disorder (e.g. 28). Thus, the lithium ion effects further strengthen a connection between manic-depressive disorder and the circadian clock system. It would be of interest to investigate whether theophylline (methylxanthine) and other substances likewise act on the circadian rhythms in man. Recently it has been shown that in the fungus *Neurospora*, lithium lengthens the circadian period of spore formation (conidiation) via an action on the concentration of FRQ – a protein that plays a central role in the feedback chains of circadian transcription-translation oscillations in this organism (31).

Circadian rhythms and clinical aspects. Light treatment

The circadian rhythms play a role also in pharmacology and therapeutics (see 32, 18). *Light treatment* can be used in some cases.

In *endogenous depression*, abnormalities in the circadian rhythms have been observed (33). Treatments affecting the light sensitivity of the retina have had therapeutic effects in such cases (34). One group of depressions is usually termed *seasonal affective disorders (SAD)*. It usually occurs as a response to seasonal shortening of the light period (35) in adults as well as in children (36) in the northern and southern hemisphere (37, 38). The circadian rhythms show,

i.a., abnormal amplitudes in this syndrome (39, 40) and the phase changes caused by light is increased (41). SAD patients are reported to be more sensitive to variations in the length of the natural day (42). A light therapy in both seasonal and non-seasonal mood disorders was successful, as reviewed by Golden et al. (43); light has accordingly significant effects for bright light treatment of SAD, dawn simulation for SAD and bright light treatment of non-seasonal depression. Typically 10 000 lux white light is reported to be used in the treatment, usually given in the morning (41). Many questions remain to be answered, before the light/SAD/clock relations are clarified (see 18). Several types of SAD are reported and light treatment does not seem to be efficient in all of them (for special literature on SAD, see 44).

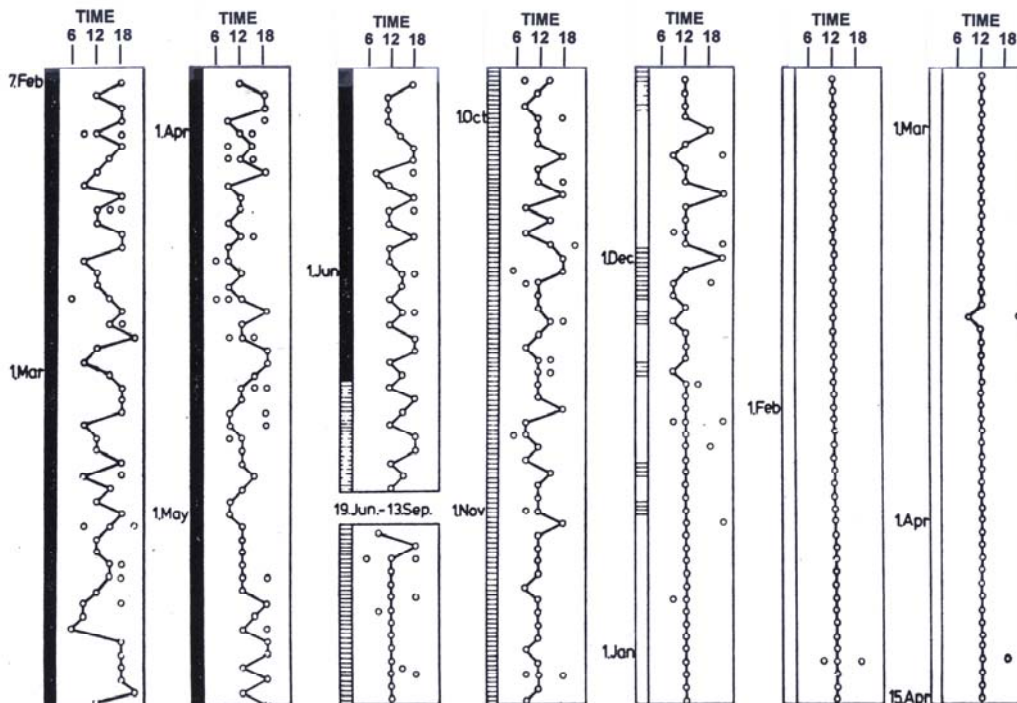


Figure 5. Daily temperature maximum of manic-depressive patient.

Seven data columns with temperature and mood plotted downwards, successively for subsequent days. Circles indicate time of day for the maximum day temperature. Self rating to the left in each column (black - self-rating 2, depressive; hatched - self-rating 1, not feeling well; white - self-rating 0, feeling well). Daily time axis given at the top above each column; date of year also indicated (adapted after (26)).

It has been discussed, whether the seasonal effects described above might reflect a photoperiodic reaction in humans (for photoperiodic reactions in humans see

45-47; photoperiodism in primates is well known (46, 48, 49)). Whether circannual rhythms play a role is not reported as far as is known to the author.

Sleep disorders are often, as depressions, connected to perturbations in the circadian rhythms and their coordination with the surrounding light/darkness patterns (reviewed by 50-52). The circadian system controls sleep structure, sleep propensity, timing of sleep, and consolidates sleep and wakefulness. Light treatment has been successfully used to treat *delayed sleep phase syndrome*. As indicated by the name, the sleep onset in the evening and awakening in the morning are delayed (53; review: 54). In the *advanced sleep phase syndrome* the symptoms are the opposite ones: sleep onset in the evening and awakening in the morning come earlier than usual. This syndrome is associated with a mutation in *per2* (55, 56). Appropriately timed melatonin treatment and/or bright light treatment were successful in the non-24 h sleep wake syndrome (57-59).

Circadian rhythms and significance of light in shift work and jet lag

The sleep/wakefulness rhythm is controlled by the biological clock as mentioned above. Our general use of artificial light sources provides an ‘artificial’ daytime as compared to the natural day. The circadian rhythm adapts by a delay but a permanent sleep deprivation might be the result. The mismatch and continuous phase changes that the circadian rhythms have to sustain in *shift work* and *night work* (experienced by about 20% in the industrialized nations) cause potential health problems (60) and safety problems arise. Many accidents are due to ill-adapted circadian clocks (61, 62). The synchronizing effect of light on the circadian system is one of the problems of shift work (63). But, on the other hand, light can be used for adjusting the clock to the shift work schedule, if properly applied (64-67).

Jet lag is the result of the slow adjustment of the biological clock to a new temporal light/darkness environment in the new time zone. Artificial light treatment might be used for adjusting the clock more rapidly (for a review of light effects on jet lag syndromes see 68; for general reviews e.g. 69-71). The flight time and duration, timing of meals etc. certainly influence prescriptions for light treatment of the jet lag symptoms. A faster adjustment after westward flights require, basically, avoidance of morning light and exposure to evening light, while an eastward flight requires light in the morning but not in the evening.

The use of melatonin to adjust the circadian rhythm more rapidly is increasingly popular. Light treatment and melatonin treatment counteract, since melatonin production is reduced by light (72, 73).

Human rhythms and exposure to light: A short summary

The action of light on the body rhythms and on the biological clocks is of paramount importance. The rhythms control a wide variety of fundamental processes in the body. These internal rhythms are usually (via the retinal perception and the clock system) showing up as daily rhythms with a 24 h period. In chronopharmacology this is emphasized by the fact that distribution of drugs or therapy is taking these rhythms into account (32). The outcome of a therapy can, as is well known, depend on its timing during the day.

If the internal clock (system) of the body is malfunctioning, different physiological rhythms might be desynchronized or even show arrhythmicity (cf. Fig. 5). This has been emphasized in the present contribution. Since the normally functioning biological clock is sensitive to light input, light treatment can be of interest to restore the proper timing of the body rhythms. We have seen that this is (sometimes) an approach, for example when it comes to depressive disorders. Light therapy can, therefore, be seen as a special form – perhaps a very important one – of chronotherapy.

It was mentioned that, in man, the light signals to the circadian system arrive from specialized retinal cells, not via the skin. The skin organ and its cells are certainly showing *daily* rhythms, and the literature provides abundant examples. Whether they are circadian in a strict sense (thus with a period slightly deviating from 24 h under constant conditions) does not seem to have been studied.

Under all circumstances light interaction with the body rhythms plays a fundamental role for our physiological and mental health and deserves to be studied in detail. A general, popular overview in Norwegian, but with reference list and English summary, can be found in (74).

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