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Biological rhythms in the context of light at night (LAN)

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> *Historical and experimental evidence indicates that human responses to seasonal changes in the natural photoperiod may have been more robust prior to the Industrial Revolution and that subsequently they have been increasingly suppressed by alterations of the physical environment.*
>
> – *Thomas A. Wehr, J Biol. Rhythms 16: 348-364 (2001)*

Abstract
In mammals including man, the most important zeitgeber for endogenous rhythms is the environmental light/dark cycle. Mammals perceive light through the eyes and that perception is relayed to the suprachiasmatic nucleus (SCN) by means of neuronal signals. The SCN, in turn, innervates the pineal gland, resulting in the production and release of melatonin almost exclusively during night-time hours. Thus, besides object recognition, eyes serve as the sensory organ for detecting the presence or absence of light. The way that light entrains the SCN is still a matter of intense research. It has been shown, for example, that the light intensities required for affecting melatonin rhythms are much higher than the intensities needed for object identification. On the other hand, even in rodents who completely lack the "classical" photoreceptors of the retina, their endogenous rhythms still can be synchronized by normal light/dark cycles. These two observations led to the hypothesis that there must be photoreceptors, apart from the known (object-identifying) retinal photoreceptors, which are responsible for the entrainment of internal rhythms. Very recently, a number of reports showed that in fact a completely new type of retinal photoreceptor, located in ganglion cells, may be responsible for entraining the SCN. It contains a photopigment, melanopsin, which shares homologies with rhodopsin, but also is evolutionarily older. Compared to rods or cones, the melanopsin-containing neurons are rare, but evenly distributed within the retina, indicating that they serve as a global, integrating light sensor. These ganglion cells apparently project directly into the SCN. Taken together, these new developments in photo-chronobiology open new areas of research. It will be of special interest, for example, to determine how the photosensitive ganglion cells and their dendrites integrate the environmental light stimuli.

ORIGINAL ARTICLE

Features of biological clocks

The physical and biological constraints of the environment of every organism set limits for its spatial and temporal orientation. Those constraints include, for example, climatic variables, presence of predators, and availability of food. As a consequence, most physiological, morphological, and behavioural processes have become adapted so that the organism fits in its ecological niche. If, for any reason, these adaptations considerably change, less optimal fitness or even death will be the consequence.

With regard to temporal organisation, many important physiological parameters show diurnal variations, i.e., having a period of 24 hours, such as blood pressure, hormone concentrations, and the sleep-wake cycle. Another type of temporal orientation relates to seasonality, i.e., the climatic changes occurring within one year, and the biological consequences. These environmental changes are caused by differences in the daily duration of illumination (photoperiod) which are more pronounced in the polar regions than at those closer to the equator (Fig. 1). The resulting variations in the availability of food present the most important limits of survival of the individual. Thus, the physiological processes have to be adjusted so that shortcomings are prevented. This is not only true for individual organisms but also for the population since the breeding period has to be limited to a specific time of the year as well.

In this context, the most important precondition for survival is that the organisms do not passively react to those cyclic environmental challenges, but rather to *anticipate* them. This evolutionary highly conserved feature allows them to act at the appropriate times (e.g., daytime, time of the year) even if the environmental parameters vary considerably. Just for illustration one example: even if a given winter is hard and cold, spring will most likely begin at the usual time. This principle of *anticipation* is realised by biological clocks whose principles are outlined below, with special emphasis on diurnal and seasonal clocks. For more detailed information, the readers are encouraged to read a comprehensive review by Rensing et al. [1].

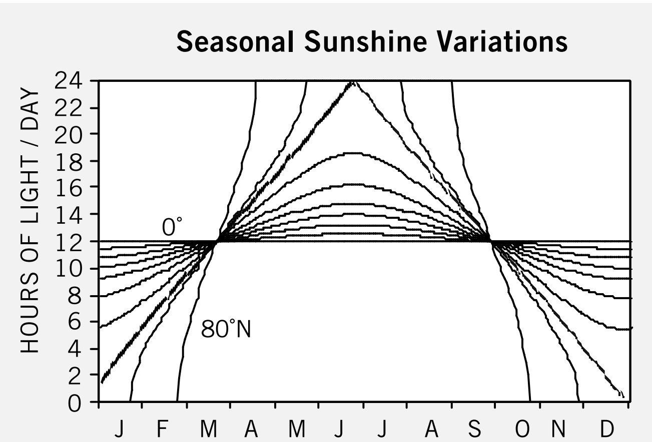

Figure 1. Annual variations of day length depending on the latitude (shown are the data for 0° N to 80° N). The dotted line represents data at the Arctic circle.

Biological rhythms are defined as oscillatory processes which repeat themselves at more or less regular intervals. Well known examples are, for instance, the sleep-wake cycle, breathing, and the heart beat. Besides these obvious examples, in fact most biological parameters show cyclic variations over a broad period spectrum, from few milliseconds (i.e., firing rate of neurons) to several years (i.e., numbers of predators and prey). Likewise, biological rhythms are seen at all levels of biological organization, i.e. from bacteria to man.

Many biological rhythms resonate with environmental physical rhythms (they are *entrained* to them), e.g., the day-night rhythm (24 hrs), and the annual rhythm (approx. 365 days), respectively. They are caused by the earth's rotation around its axis, and by its rotation around the sun. While the rotation of earth causes day and night, the angle between the earth's own rotation axis and its rotation plane around sun is the reason for different day lengths throughout the year (Fig. 1). But also the moon influences many organisms, especially in coastal regions, where the tidal rhythm (approx. 12.5 hrs) and the lunar rhythm (approx. 28 days) are very important external events for the respective organisms.

The proof for the existence of biological rhythms are experiments where the cyclic environmental parameters are either not present or not conceivable by the organisms investigated. Such *temporal isolation* experiments were actually performed as early as 1729 by de Mairen who showed that prayer plants, when exposed to constant darkness (DD), continued to show leaf movements like those plants exposed to the normal light-dark (LD) photoperiod. In plants, the duration of DD experiments is limited by the plants' need of light for photosynthesis, but animals may spend their entire life under DD conditions (Fig. 2). Both animals and plants can also be exposed to constant light (LL), likewise with the result that free-running rhythms occur.

Effects of light at night

If animals are exposed to even very brief light pulses during a DD experiment, specific changes of the activity patterns occur (Figs. 3 and 4). Depending on when during the animal's subjective night these light pulses are applied, either phase advances or phase delays result. In the context of the question whether or not artificial light is a possible carcinogen, it is important to note that the resulting shifts in activity are representative of many other physiological and endocrine phase shifts which, in turn, may feedback to the master clock (see below). Likewise, these shifts are not compensated by shifts in the opposite direction during the following nights.

It is possible to fully entrain animals to a 24 hr period exogenous light dark cycle even if a short light pulse is given only once per 24 hours. Even if this "skeleton" photoperiod consists of light pulses given only once per week, entrainment is possible. Thus, even very brief and rare light pulses are able to profoundly affect the endogenous clock.

This was also seen in hamsters which were exposed to brief night pulses during the middle of the night (Fig. 5). Acute exposure (group A) caused a drastic drop in mela-

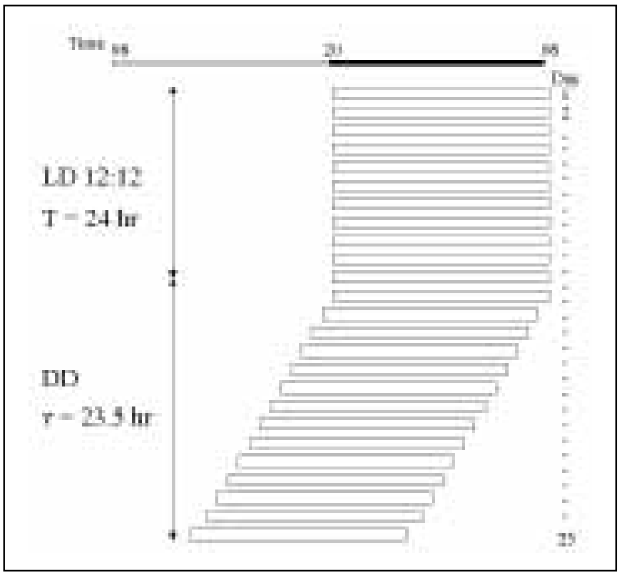

Figure 2. Illustration of free-running rhythms. In this case, a nocturnal animal was first exposed to a LD 12:12 light dark photoperiod with lights off from 2000 hr to 0800 h (solid bar). The resulting activities (open bars) were synchronised with the environmental LD cycle and had a period (T) of 24 hrs. After transition to DD, a free-running circadian rhythm developed with a period (τ) of 23.5 hrs.

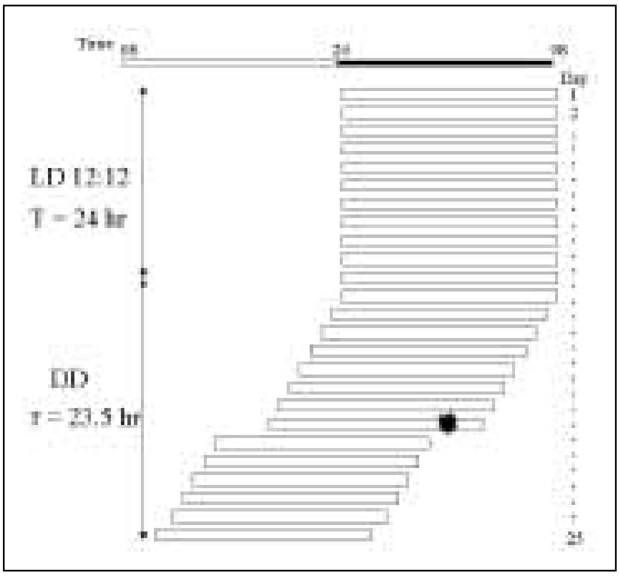

Figure 3. Effects of a brief light pulse during the activity time of a nocturnal rodent. When this light pulse (asterisk) is given late during the activity period (late subjective night), the activity onset is shifted to the left (phase advance).

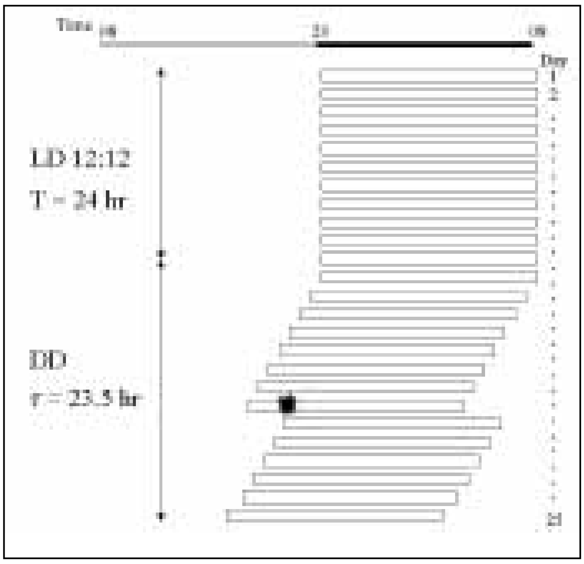

Figure 4. The same situation as shown in Fig. 3, except that here the light pulse is given at the beginning of the activity period (subjective night). In this case, the activity shifts to the right (phase delay).

tonin from the pineal gland without recovery during the late phase of the night. Most interesting was the finding in an additional group (B) of hamsters which had been exposed to the same light pulse one night earlier, and not during the night during which they were sacrificed. Here, the drop of pineal melatonin was also present at the same time as in group A, but it was even more pronounced, indicating that the melatonin generating system has a "memory" for previous light exposure. Thus it is evident that even short light pulses can have strong effects 24 hours later.

The components of biological clocks in mammals

For a functioning and entrainable biological clock the following components are essential: a receptor for environmental signals, a pacemaker which oscillates with a specific frequency, and an effector, e.g., the pineal gland, which produces a distinct rhythm (Fig. 6). In some cases, the rhythm may feed back to the pacemaker. In mammals, the most important zeitgeber for biological clocks is the environmental photoperiod which is perceived by the eyes and relayed to the suprachiasmatic nucleus (SCN), the seat of the master clock. From there, specific neurons project to other areas of the brain, e.g., the hypothalamus.

The SCN consists of small, densely packed neurons which are working in synchrony. Within each neuron, a complex interaction of transcriptions of clock genes, and positive and negative feed back loops exists which results in stable circadian rhythms [3, 4]. If the SCN is destroyed in rats, diurnal or circadian rhythms are no longer present. If the input pathway is blocked, e.g. by removing the eyes, the endogenous rhythm in no longer entrained by the photoperiod and starts to free-run. In this case, or when animals are kept under constant photoperiods (LL or DD), melatonin injections given at regular intervals are able to resynchronise the free-running rhythms to 24 hrs. In blind people very often additional sleep and social problems exist which are caused by free-running rhythms of their biological clocks. It was shown that those humans benefit from melatonin when administered before bedtime [5–9]. In most cases, their rhythms can be re-synchronised to the 24 hrs period length. See also a recent review by Wehr on photoperiodism in primates and humans [10].

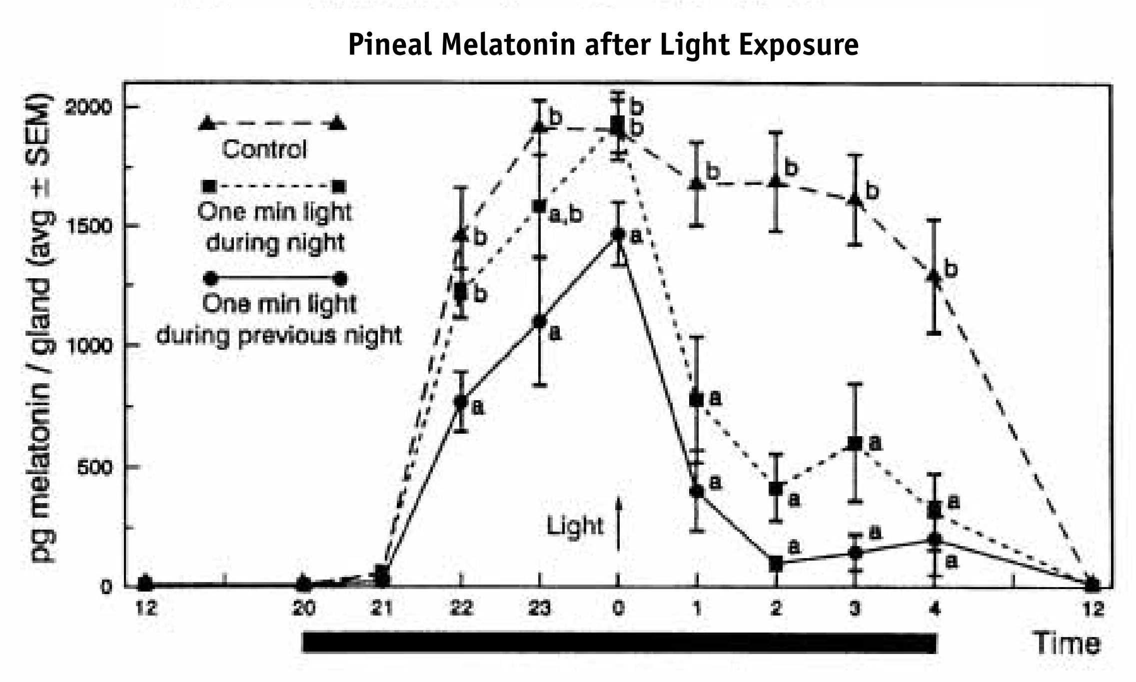

Figure 5. Effects of brief light pulses (1 min) on pineal melatonin concentrations in Djungarian hamsters (*Phodopus sungorus*). While acute exposure caused the expected immediate drop in melatonin concentration, the same effect, even more pronounced, was seen when animals were exposed to a single light pulse one night earlier. Thus, the melatonin generating system including the master clock must be able to memorise previous light exposure. Data from Lerchl, 1995 [2].

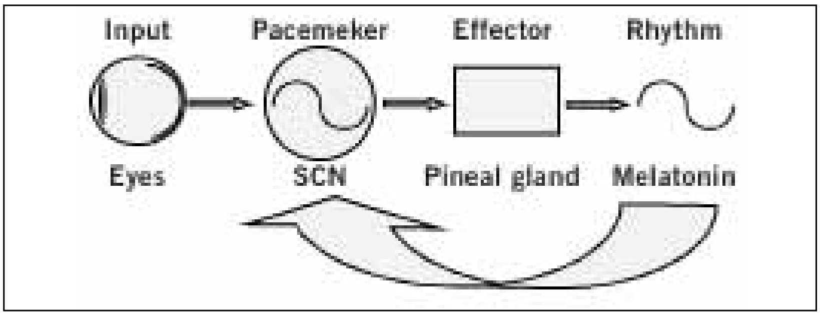

Figure 6. Components of the mammalian biological master clock system.

Photoreceptors for photoperiod

It is long known that the input for the SCN is located within the eyes since removal of the eyes results in a free-running rhythm if photoperiodic signals are the most important zeitgebers. However, there are at least two major concerns. First, the light intensities needed for synchronisation are usually much higher than those needed for vision. Second, rodents lacking the classical photoreceptors are blind, not able to perform the simplest vision-based behavioural test, but perfectly entrainable to LD cycles. Thus the question was whether there might be non-rod, non-cone photoreceptors in the eyes which just sense the photoperiodic information rather than being responsible for vision. In fact in 2002 such putative novel photoreceptors were identified which are located in the ganglion cells. They seem to directly project into the SCN and set the circadian clock. Their photopigment is melanopsin, an evolutionary older molecule than rhodopsin. Further details are found in the paper by Brainard in this issue [11]. Our group was recently able to identify the structure of melanopsin of Djungarian hamsters (Lerchl et al., in prep.). The stucture homologies to rhodopsin also speak in favor of a role of melanopsin as a photopigment.

Seasonal rhythms and secular trends

As indicated earlier, many organisms show pronounced annual variations in terms of physiological adaptations and reproduction. These seasonal rhythms are regulated by the photoperiod via the annual changes in the production of melatonin since long days (summer) are associated with a short melatonin synthesis duration, while in winter melatonin synthesis is considerably longer. Exogenous melatonin or pinealectomy can mimic winter and summer conditions, respectively [7]. In humans, annual variations of melatonin synthesis duration have also been shown [12]. Although humans do not show distinct breeding seasons like many other mammals, there are clear seasonal rhythms in birth rates in most countries investigated so far [11–13]. Interestingly these rhythms, being stable presumably for millenia with conception peaks in spring / early summer, have changed during the last 50 years, and in some countries they are now phase-reversed with conception peaks in winter [13–15]. The reasons for these secular trends are still unclear, but it is possible that industrialisation has led to a photoperiodic environment which may be the explanation for the observed trends. This theory can be tested in further investigations.

Summary / Conclusions

Biological clocks are an essential prerequisite for successful adaptations to cyclic, but often unpredictable changes of environmental parameters. Instead of passively reacting to those challenges, organisms can anticipate what (most likely) will happen in the future, be it during the next hours or during the next months. Almost all physiological parameters show clear diurnal and annual variations which persist even in the absence of the respective zeitgebers. In mammals, the most important zeitgeber is the photoperiod, causing diurnal and seasonal variations in the duration of secretion of melatonin from the pineal gland. Light at night, even very short light pulses, cause long-lasting effects with the biological clock working as a memory system. Biological clocks using light as the predominant zeitgeber have evolved in the *absence* of artificial light, and thus modern illumination scenarios with light at night certainly affects the biological rhythm generating system and all secondary rhythms. Whether or not these consequences of modern life have adverse health effects remains to be seen, but the well founded possibility of such outcomes, possibly affecting billions of humans, deserves highest priority in political and scientific decision making.

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