Our internal clocks
Biological timing in humans and other mammals

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Introduction

Most humans are able to orient themself quite well even in an aerea unknown to them. They use their senses which are well established for recognizing the environment, to store it and to recall the internal map. This is so well known to us, that we seldom pay attention to it. It just works.

Additionally we possess a good time memory. It helps us to perceive intervals, to remember time points and to plan the future. These abilities to orient ourself in time are even less appreciated by us as is the ability to orient spatially, although they are at least as fascinating. Therefore I would like to talk in this book about internal clocks of humans and other mammals.

In an overview I will begin with some examples for the performances of our internal clocks and their usefulness. There are first of all the numerous processes in our body, which show a daily rhythm: Sleep and wake, activity and rest, varying body temperature, metabolism and hormones. Why do these processes occur rhythmically? What is their purpose? How are they produced by the body and where are the centres of their control? How are these rhythms synchronized with the 24 h day? What is their significance for healthy and sick humans? These are questions, which will be dealt with in later chapters.

How daily rhythms are brought about by the organism can not be studied very well in humans. Better suited are animals, which can be used for experiments. Rodents such as rats, mice and Syrian hamster are especially qualified. They can be reared easily, breed rapidly and prolific, and mutations are available in which the daily rhythm is altered. Rodents are therefore used to study the mechanism of these clocks.

Animals can also be used to study, how they adapt to the changes of the seasons. As you know, there are enormous differences in the temperate and higher latitudes of the earth in respect to food availability and daylength. The behaviour of the animals changes accordingly. Propagation is restricted to a certain season and different strategies for surviving the winter are used.

Back to humans: Are seasonal adaptations also known in man? Monthly rhythms -wide spread in organisms in and at the sea- are found also in humans. The daily rhythms play, however, a much more important role. They have penalties at shift work and travelling through time zones. The kind of penalty and what one can do against it will be discussed. Medical aspects will also be treated.

1 The internal clocks of humans and other mammals, their performances and advantages

Many processes in nature are rhythmic. The daily revolution of the earth around its axis and the annual orbit around the sun lead to day and night, summer and winter. The orbit of the moon around the earth leads to tides and the interplay with the sun to monthly rhythms. These physically caused rhythms change the habitat of the organisms strongly, but regularly. The organisms have adapted to it and are able to imitate the external rhythms with internal clocks .

How does one detect, whether a clock (or several) is working in an organism? It is not sufficient, to verify, that a process (for instance tiredness) occurs each day at the same hour and continues for some time, because the process could be controlled directly by the environmental cues. Thus, a person could become tired a few hours after onset of darkness. But there is already one problem: Not all humans become tired at the same time, and in the summer with its longer light periods sleep would begin later as compared to the winter with shorter light periods.

Here an experiment will help us. We spend a few days in a room which is free from external time cues (for instance a cave or a room well insulated against sound). We do not take a clock along, nor telephon or radio or TV. Light is on all the time during our stay in isolation. We have thus no time-cue of the outer world. A person in charge, however, is able to record via electrical signals our behaviour and the state of our body (walking around, sleep, body temperature). It turns out, that we possess still a daily activity rhythm, that we have still our regular seven to eight hours of sleep and that our body temperature alternates periodically by about half a degree.

If these data are potted graphically (figure 1.1), we will make two buffling discoveries: First, the records continue to alternate in a daily rhythm. Secondly, the variations do not follow an exact 24-h-cycle, but are slower. For instance, in a particular person it might run in a 24.7 h-cycle. Each day this person would fall asleep in his isolation facility 42 minutes later and rise up later for the same amount of time. At the same time the rhythm of activity and of body temperatur would be extended by 0.7 h. If the rhythm would have continued to follow a 24-h-measure, we might suspect, that in spite of the isolated room some kind of time cue concerning the time in the external world might have been perceived by the person. Since, however, the period length (which can be determined for instance by measuring the time from falling asleep to falling asleep on the following day) has increased (in our fictive case by 0.7 h), an internal clock must control the rhythms of the body.

This clock is normally synchronized by environmental conditions to exactly 24 h

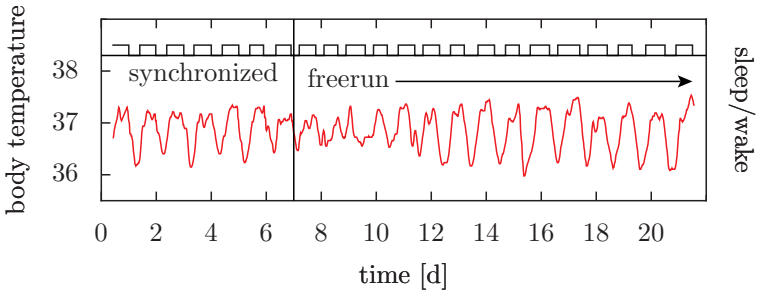

Figure 1.1: *Course of the body temperature of a person under synchronisation by the 24-h day (first part, 'synchronized') and under freerun (second part, 'freerun'). Top curve shows wake- (boxes) and sleep periods (empty). After Aschoff (1981)*

(left part of figure 1.1). Its true character is shown not before the time cues of the external world are screened: It is a self-contained clock with its own period, which does lie close to 24 h (circa 24 h), but is not exactly one day long. Therefore this clock is called circadian clock (circa dies, about a day).

We will now see, what this circadian clock controls rhythmically im humans. We choose the sleep-wake-rhythm, the activity rhythm (xx), the rhythmic variations of the body temperature, the rhythms in metabolism (xx) and hormonal rhythms.

1.1 Sleep and wake

If we have become 60 years old, about 20 years of it we have slept, since we sleep about 8 h per day. Sleep is thus the most frequent occupation of humans and essential. Sleep deprivation for longer periods is harmful or even fatal (Everson et al. (1989)). Like humans most mammals spend a large part of their life sleeping (Campbell and Tobler (1984)). In spite of its common occurrance the physiological basis of sleep is only insufficiently known, although much work is done in this field (Nicolau et al. (2000)).

Why do we sleep? This is a very complex question. Sleep probably evolved in mammals and birds in connection with the evolution of the anterior brain to a multilayered neocortex (mammals) or neostriatum (birds). The brain had to cope with two different kinds of the wake state:

1. The older one was responsible for the activity during the light period. In mammals this original type of waking state, which is under the control of the brain stem, was suppressed (and was conserved as a *non-active* state in the 'slow wave sleep´).

2. A more recent type of waking state was assigned to the cortex of the brain, after homeothermy was invented and a nocturnal way of life began to dominate in mammals. The nocturnal resting period of poikilothermic animals might have remained as a residual in the REM (rapid eye movement) sleep of homeothermic mammals.

The complex structure of mammals is according to this conception only a residual of evolution. The control of the waking state by the cortex is thus the actual innovation in mammals.

A number of proposals was put forward to explain, why we sleep:

1. Sleep occurs automatically after a certain time of waking. If we (or an animal) were active for a certain time of the day, we get tired and fall asleep. This was tested experimentally. Rats had access to running wheels, in which they normally run up to seven kilometers per night. Was admittance refused, they still slept as usual. Activity during waketime does accordingly not induce sleep. On the other hand sleep demand was increased, if the wake time was longer.

2. During sleep less energy is used. Sleep could accordingly reduce energy consumption and prevent in this way exhaustion. Against it speaks, what was said under point 1.

3. Sleep conduces recreation. During sleep the central nervous system is maintained and repaired.

4. It was also proposed, that we sleep, in order to avoid dangerous situations during the night which arise due to darkness, coldness and enemies.

5. Do we sleep, because it is time for it? In favour of this proposal speaks the observation, that from a critical time point in the morning onward tiredness dissappears, if we did not sleep in the night.

Possibly several of these proposals are valid. For us the last point (5) is especially interesting. Tiredness varies in a daily rhythm (figure 1.2). That the sleep-wake-rhythm of humans and other mammals is controlled by the circadian clock, shows up under conditions, in which time cues are absent (no light-dark-changes, no temperature changes, no time information). In spite of it the sleep-wake-cycle continues. However, the period of this rhythm is no longer precisely 24 h. In most humans it is longer than 24 h and amounts to 25 h as a mean value (range from 23 to 28 h).

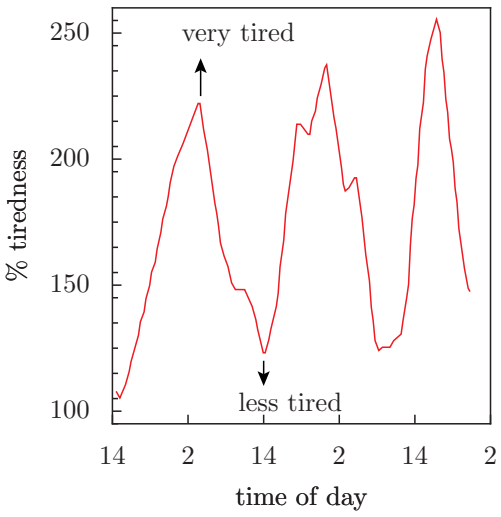

Figure 1.2: *Circadian rhythm of tiredness during sleep deprivation. Fifteen women were kept awake for 72 h . They reported every 3 h, how tired thes felt (mean value of normal tiredness 100%). After Åkerstedt and Fröberg (1977)*

For literature concerning the circadian control of sleep and its time structure see Webb and Dube (1981).

1.1.1 Physiology of sleep

Phases of activity and rest follow each other not only in vertebrates, but also in lower animals such as molluscs and insects and even in unicellulars. These rest periods in lower animals could be the precursors of the sleep-wake-rhythm in vertebrates. They are normally under circadian control. However, according to Borbely (1982), this cir-

cadian control of the rest period is too rigid. Therefore higher animals use a special process which controls sleep, depending on the external conditions, much more flexible as the rest-activity-cycle does (see subsection 1.1.2).

Most adults in many western countries adopted a sleep pattern, where they sleep in one piece throughout the whole night without any rest period ('siesta') during the day. There are, however, countries, where people have a siesta in the early afternoon. This pattern is probably more adequate to the needs of the body. In any case it is recommendable to stick to a certain pattern (Rappelsberger et al. (2001)). Apes have 5 to 6 rest- and sleep-periods per day.

Pieron (1913) defined sleep as a necessary process, which occurs rhythmically and more or less independent of external conditions. In this state sensory and motoric interactions of the brain with the environment are interrupted. In the meantime it is known, that during certain sleep stages sensory informations of the periphery reach the cortex, and motoric signals of the cortex get to the α-motor-neurons of the spinal cord, although the efferences of the motor neurons do not work. Sleep is thus not just an idling process, but an active neuronal process, in which different psycho–physiological events follow each other periodically. They are controlled by different neurochemical systems (Kandel and Schwartz (1991) and Borbely et al. (1999)).

During sleep the physiology of the body changes considerably. A very reliable method, to recognize sleep, is the recording of electrical potentials from the skull (electroencephalogram EEG) or from the surface of the cortex (ECoG). The signals are plotted and sorted according to the various frequency components (Hoofdakker (1966)). Different phases with various components alternate with each other. They belong to the different sleep phases, which consist of slow wave sleep (SWS) and rapid eye movements (REM) and are illustrated in figure 1.3. About 30 to 45 minutes after the end of the wake state the stage of SWS with the deepest sleep begins. It takes another 30 to 45 minutes, to come back to the flattest SWS. A REM-stage follows, before the various SWS-stages are repeated. SWS and REM alternate 4 to 6 times per night. With advancing night the REM-episodes become longer and the intervals between them shorter. In the young adult about 25% of the sleep belong to REM, about 50% to the SWS-stage 2. The stages 3 and 4 occur mainly in the first part of the night, the flatter SWS stages 1 and 2 and the longer REM-stages occur in the second part of the night.

During the SWS the muscles are relaxed, but the body is still active. Thus, for instance, the position of the sleeper changes about every 20 minutes (in some persons even in shorter periods, for instance every 5 minutes). Parasympathic activities dominate. Heart beat and blood pressure are reduced, the gastrointenstinal activity increased. With increasing deepness of sleep it becomes more and more difficult to awaken the sleeper.

Differences in the length of sleep are compensated by the intensity of the sleep (deep sleep stages 3 and 4 of the SWS are more pronounced. This is also called 'sleep-homeostasis´, because this intensity component warrants enough sleep).

The neurophysiological basis of EEG signals have been studied intensively (Steriade et al. (1993)). The dominant frequencies of the 'slow-wave sleep´- EEG (slow waves and spindle-oscillations) correlate well with waves of the thalamocortical neurons. At the transition of the brain from the wakeness– or REM-stages (desynchronized!) to the slow-wave sleep (synchronized!), the membran potentials of the thalamocortical neurons hyperpolarize. Further-

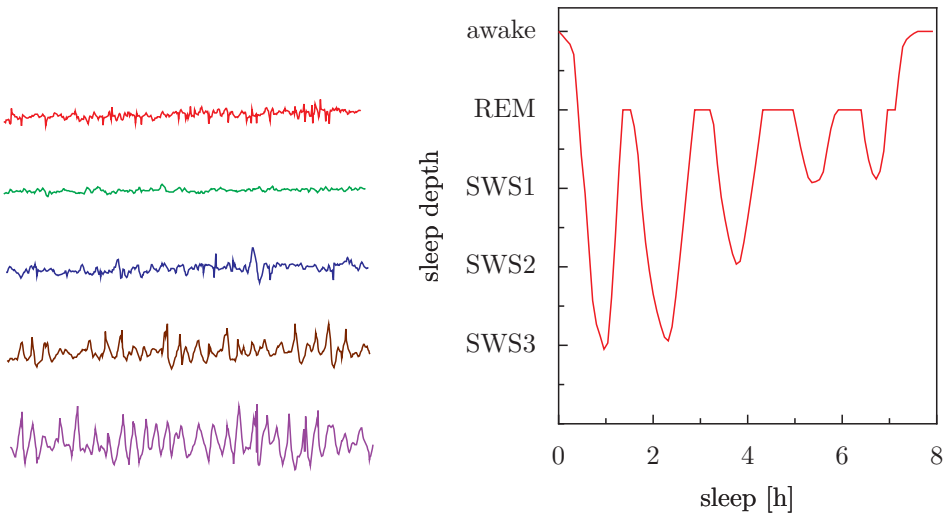

Figure 1.3: *Left: The electroencephalogram pattern of humans in the wakeness state (red) and in various sleep stages (REM-sleep green,* slow wave sleep *SWS 1-3 blue, brown, purple, length of each curve 30 seconds). Right: Sequence of SWS and REM during sleep. After Kelly (1991b)*

more these neurons begin to fire in rhythmic bursts. Calcium-inflows and sodium-mediated action potentials are involved. These processes correspond to the observations of the EEG (Aeschbach and Borbely (1992)).

Recent studies (Gallopin et al. (2000)) show, that a certain group of cells in the ventrolateral preoptic nucleus (VLPO) of the preoptic area has a sleep-promoting function. It is a homogenous group of cells, which are inhibited by monoaminergic and cholinergic neurons of the wake system during awakeness. They are thus *inactive* during awakeness. At the onset of sleep these neurons begin to increase the fire frequency under the influence of circadian inputs of the retina and the SCN and under the influence of homeostatic factors (body temperature) and sleep-promoting factors (Edgar et al. (1993)). The increasing activity of its GABAergic neurons inhibits the wake-centres, to which they project. They are therefore less inhibited by the wake-centres and the activity increases further. All this facilitates the promotion of sleep by the neurons (Gallopin et al. (2000)).

Further cell groups with similar properties could be present in other areas of the basal anterior brain and the preoptic region. But retinal and SCN-inputs are found only in the ventrolateral preoptic nucleus.

The genetic and molecular control of sleep in mammals is currently also studied, for instance by looking for ‘sleep-genes´ (Kolker and Turek (1999)).

1.1.2 A model of the sleep-wake-cycle

Models allow to represent complicated systems in a simpler way. Whether they are useful can be checked by using the models for predictions which are afterward tested by experiments. If the predicted results are not found, the model has to be changed and tested anew.

Such a model for the sleep-wake-cycle was proposed by Daan et al. (1984) (see also Daan and Beersma (1984)). A circadian rhythm c (sleep-independent) and a

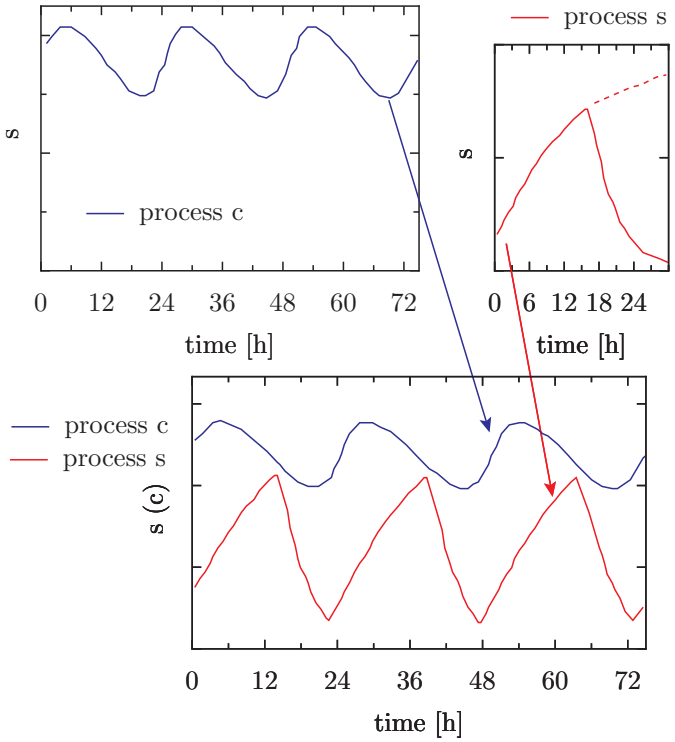

Figure 1.4: *A two-process-model of sleep regulation: A circadian rhythm (process c, sleep-independent, blue curve) and a homeostatic process s (sleep-dependent, red curve) interact with each other. A fall-asleep-threshold (the red curve touches the blue one) and a threshold for wakeup (the red curve touches a threshold in its lowest point) are thereby important. The model was checked in rats and humans. After Daan et al. (1984), see also Daan and Beersma (1984)*

homeostatic process s (sleep-dependent) interact with each other. A threshold H determines, at what time we fall asleep, and a threshold L, at what time we wake up (see figure 1.4). The model was tested successfully in rats and humans.

1.2 Rhythmic variations of body temperature

How the body temperature is controlled in homeothermic animals is described on page 9. The course of temperature is not constant, but fluctuates in a daily rhythm around a mean value. This rhythm is determined by an internal clock, since it is present also under constant conditions of continuous light and constant environmental temperature and because it does not depend on the activities of the animal (figure 1.1).

Between 1967 and 1990 about 2700 publications appeared on circadian rhythms of body temperature, more then 100 per year. An article by Refinetti and Menaker (1991) gives an overview.

The heat *production* contributes with 25% to the rhythmic fluctuations of the body temperature, the heat *dissipation*

(skin, blood circulation, poorly insulated parts of the body such as extremities) with 75% (the values depend on the external temperature). Especially the *heat dissipation* is under circadian control. The body temperature- and skin temperature-rhythms differ from each other in their phase relationship to each other (see figure 1.5). Changes of the blood circulation to and from the skin of the extremities, differences in the central reference points and the sensitivity or efficiency of thermoregulatory effector mechanisms play a role. Additionally the behaviour feeds back and contributes to the differences.

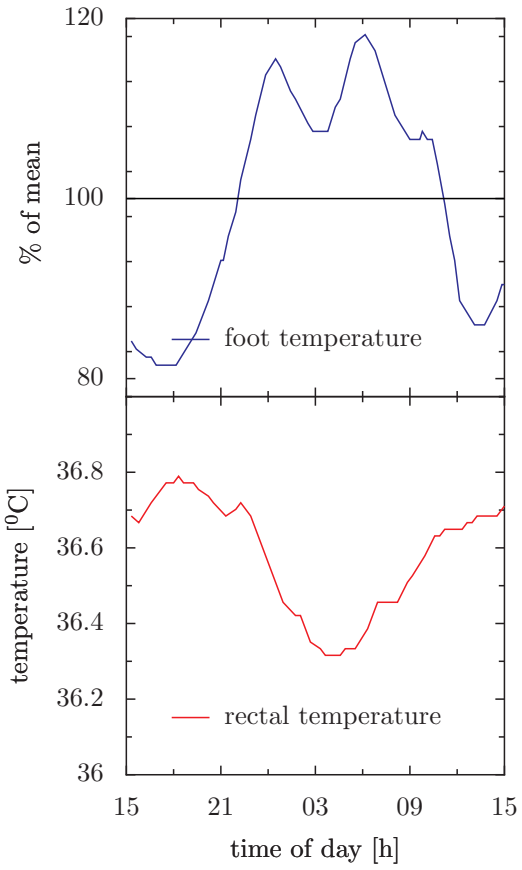

Figure 1.5: *Core temperature- and foot temperature-rhythms differ in their phase relationship to each other: Whereas the core temperature (measured in the rectum, in degrees Celsius) is higher during the day, the foot temperature is higher during the night (deviations from the daily mean, in percent). After Hildebrandt et al. (1998)*

Under constant conditions and without time cues the period length of the body temperature amounts to 25 h as a mean. In contrast to synchronized conditions the body temperature rhythm is advanced by 4 h in respect to the activity rhythm[1].

The body temperature course is often biphasic, with a dip around noon (figure 1.6, Aschoff (1966)).

Why does the rhythm of the body temperature exist at all? The energy saving is at least in larger mammals too small (namely 260 kJ per day at 1^0C amplitude). This is less than 3% of the 2400 kCal per day. Furthermore this temperature difference exists also during hibernation in the course of the day. The question posed can not be answered so far.

1.2.1 Control of body temperature in mammals

Mammals and birds possess a more or less constant body temperature. In spite of varying temperatures in the environment it is kept constant to a few degrees (homeostasy). By an increased metabolism endothermic heat is produced. In addition the fur of mammals promotes thermal insulation[2]. Furthermore animals are able

[1] but not in all animals. In animals the circadian rhythm of the body temperature damps out in conditions without time cues. Likewise the activity rhythm and the drinking rhythm are damped. Damping is perhaps brought about by desynchrony under constant conditions. The rhythm can be restarted.

[2] in huskies it is so perfect, that they are able to sleep outdoors even at -30^0C without increas-

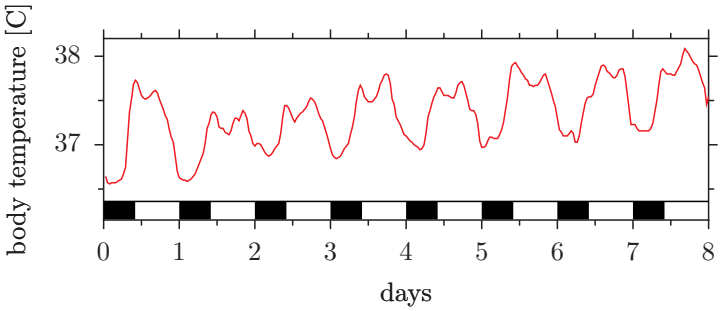

Figure 1.6: *Biphasic course of body temperature of humans, with a dip in temperature around noon. Increasing mean of body temperature caused by the estrus cycle. After Moore-Ede et al. (1982)*

to isolate themselves against the environment by laying out subterranean passages and nests and to hoard food.

Of high significance is in homeothermic animals a constant brain-temperature. The body temperature of an antilope can increase up to 44^0C, but the brain-temperature does not surpass 40.5^0C. A special heat exchange-mechanism takes care of it (Baker (1979)). The temperature regulation begins, when the hypothalamus-temperature deviates from the reference value by 0.5^0C. This regulation occurs also during torpor and hibernation, but at another set point. During REM sleep temperature-regulation does not occur. During the SWS the set point of temperature-regulation is by 2^0C lower as compared to the wakeness state.

Why do birds and mammals possess such a high body temperature? Probably at the time, at which the mammals arose, heat dissipation was the main reason: Heat can still be dissipated at high body temperature even at a high external temperature by utilizing the cooling effect of evaporation (panting, sweating). An advantage of homeothermy is, that it allows animals to be much more persistent and able to react immediately to extreme conditions during the day or the seasons. They have to pay for it, however, by a twice as high energy demand.

1.2.2 Physiological basis of temperature regulation

Die physiological basis of temperature regulation and of homeostasis are briefly presented in the following (for an overview see Bligh (1973), Cabanac (1975), Cossins and Bowler (1987), Hensel (1981)).

Temperature constancy means, that heat production and heat loss balance each other (Bligh (1973), Boulant (1981) and textbooks on physiology such as Kandel and Schwartz (1991)). Heat is mainly produced during metabolism and can increase at high activity by a factor of 10. Therefore mechanisms, which dissipate heat, are very important. Heat dissipation depends heavily on external conditions such as temperature and wind. Three different mechanisms of heat dissipation exist:

1. Heat conduction

2. Heat dissipation

ing the metabolism perceptibly

3. Cooling by evaporation.

Heat conduction and heat dissipation are only possible at lower environmental temperatures. Especially effective is convection, at which flow is induced naturally (thermal) or forced (by wind). The 300 K warm body radiates independent of the colour of the skin and fur. The heat dissipation is most important for cooling the body. It is used by sweating and panting. During heat balance the heat production of the metabolism (in resting humans 70 kcal per h) is evened out by the sum of the three heat dissipating mechanisms.

Heat production occurs with 56% in the organs of the chest and abdomen, although they add only to 6% of the body mass. Heat production occurs thus mainly in the core of the body and not in the periphery (skin, muscles). Due to the work of muscles the metabolism and hand in hand with it the heat production is increased ten-fold.

What about the control of the body temperature? The surface of the body passes through relatively high temperature differences, whereas they are small in the core. The goal is, to keep the body temperature close to the set value (Bligh (1973)). Two control systems exist:

1. Thermal skin receptors in the shell of the body: The first defense line against coldness and heat. Here we are dealing with a broad band control system. It influences the peripheric circulation by the vasomotoric tonus (vaso-constriction and vaso-dilation).

2. Thermoreceptors in the core of the body (hypothalamus). They regulate sweating and dithering and constitute a further defense line against heat. It is a small band control system.

In figure 1.7 this control system is shown schematically. For studies the body temperature is recorded with sensors which transmit the signals via cables or telemetrically (in the case of intraperitoneally implanted sensors). Infrared-pyrometers are also used. The rectal temperature is usually used, but the tympanal temperature is also quite close to the body temperature (deviates not more than 0.2^0C, measured in persons which were exposed to coldness).

1.2.3 Body temperature and sleep-wake-rhythm

Normally body temperature- and sleep-wake-rhythm have the same measure. But the circadian rhythm of activity and body temperature do also run parallel. Usually the maxima of body temperature and of activity occur at the same time. But under certain conditions they are not coupled and can part from each other, which is called internal desynchronisation (figure 1.8). It was concluded that several oscillators are coupled with each other.

There are further indications, that the circadian rhythm of body temperature is not just a passive consequence of activity:

1. The circadian rhythm of body temperature is advanced in respect to that of the activity, temperature is thus already increasing before rising up.

2. Although the body temperature decreases at the time of falling asleep, this amounts only to 10% of the amount by which it fluctuates during the whole temperature cycle.

3. Confinement to the bed during the entire day reduces the circadian rhythm of body temperature (amplitude) only slightly more than usual. That is also true, if no food is taken in for 24 h.

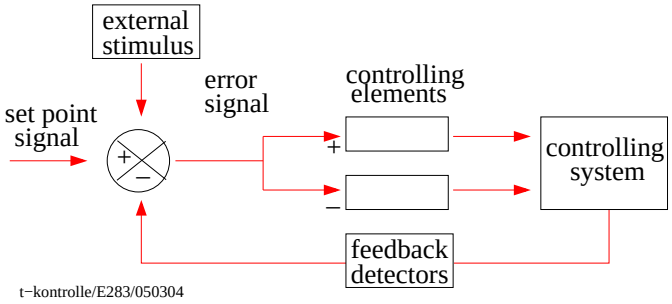

Figure 1.7: *Control system of the body temperature (and many other homeostatic processes). The signal of a reference value (here: mean body temperature) is compared with an afferent signal of the controlled system (here: Temperature receptors of the skin, the hypothalamus and other parts of the body). If differences exist, an error signal is sent to positive (heat production) respectively negative (heat dissipation) control elements, which influence the controlled system*

4. Under sleep deprivation for several days the circadian rhythm of body temperature is not lost.

5. Morning types and evening types show a very similar body temperature rhythm, although the activity rhythm differs.

6. During continuous activity and food taken up uniformely spread over the whole day, the circadian rhythm of body temperature is conserved. Only the amplitude is somewhat reduced.

Apparently body temperature and activity are controlled by separate oscillators.

Does the circadian control of body temperature affect the reference point of temperature, that is, is the set point changed during the course of the day? A number of results speak in favour of it (Refinetti and Menaker (1991)). For instance, the body temperature fluctuates in a circadian way, even if a person sleeps very long (during an illness). During fever the set point of temperature is increased by boosting heat production and reducing heat dissipation. The body is thus much more complicated as compared to a thermostate made by engeneers. It does not possess a fixed set point, but it is influenced by internal and external factors.

Alternatively circadian rhythms of the body temperature could very well also come about by a rhythmic control of the heat production and heat dissipation and not necessarilyby a set point which is changed in a circadian way (Robinson and Fuller (1999)).

1.3 Hormonal rhythms

The endocrine system of humans is also under circadian control. However, some hormones are secreted also in an ultradian pattern such as for instance the sexual hormones LH and FSH.

Figure 1.9 shows the scheme of the rhythmic control of hormones in the case of cortisol and conjugated corticosteroides. Cortisol and conjugated corticosteroides are the most important corticosteroides of mammals. Corticosteroides are made from cholesterol in the adrenal cortex. The

cortisol-concentration is high in the morning and low in the evening. A minimum is reached in the first two hours of the sleep. In man maximal concentrations occur during the time of awakening. Afterward it decreases until about 1-2 h before onset of sleep. If every 20 minutes blood samples are taken with a catheter and tested for corticosteroides, 6-9 episodes are found per day, which is an ultradian rhythm (see figure 1.10) superimposing a circadian rhythm. This rhythm is neither influenced by behaviour nor by the rhythmic environmental conditions. It is namely found also during continuous rest in bed, during sleep deprivation and during uniformely applied food. The rhythm does not yet exist in newborn children. It takes 2 to 3 years until it is established.

In the absence of time cues the cortisol rhythm in the plasma shows a period length of 25 h. It has the same length during internal desynchronisation. The most important time cue of this rhythm is the light-dark-cycle. In humans blind from birth onward the cortisol rhythm shows occassionally freerun. Stress increases the cortisol concentration. This masks the rhythm. It was shown in rats, that the corticosteroides are secreted rhythmically also in vitro (Ottenweller et al. (1979)).

The amplitude of the growth hormone GH is high and fluctuates around 100%. The maximum occurs in the first two hours of sleep. Its time course is independent of cortisol and insulin. Aldosterone and prolactine fluctuate by 50%, the maxima and minima occur at the same time as those of cortisol. Testosterone and tyrotropine fluctuate by less then 20%. LH and FSH show especially pronounced ultradian bursts. LH exhibits in women a menstrual and a circadian rhythm.

Daily rhythms influence also the time of birth. More babies are born between 3 and 4 o'clock. If fertilized eggs are implanted in women, it is only successfull between 22 and 24 o'clock (in 4 out of 79 cases).

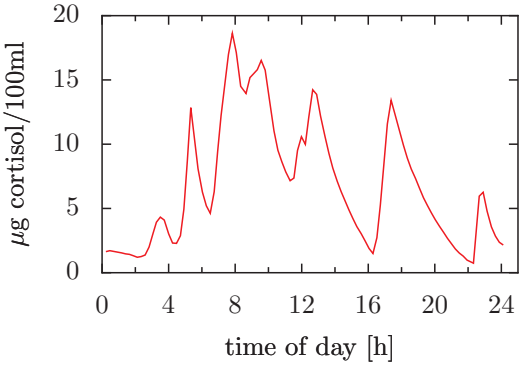

Figure 1.10: *Daily course of cortisol-concentration in the blood plasm of a patient. Every 20 minutes a blood sample was taken with a catheter. After Moore-Ede et al. (1982)*

1.4 Why are these processes rhythmic?

Many processes in nature are rhythmic. Think of the daily changes of the light conditions and the temperature caused by the revolution of the earth or the tidal rhythms and neap-and spring tides caused by the orbiting moon. All complicated systems tend to oscillate, from sand waves in the dessert and structures to processes in organisms. It is therefore not surprising, that we find rhythms in all lower organisms, plants and animals. It is, however, special, that organisms use these rhythms for their advantage.

For instance, certain metabolic processes, which can not occur simultaneously, can well proceed if they occur sequentially. Rhythmic processes allow the organisms, to predict certain events in the environ-

ment and to prepare for them in their metabolism and behaviour. Rhythmic processes are as a rule also more stable as compared to uniformly occuring ones. In some cases it has been shown, that mutants, which lost their daily rhythm by a mutation, possess a lower selection value as compared to the wild type with a functioning day clock.

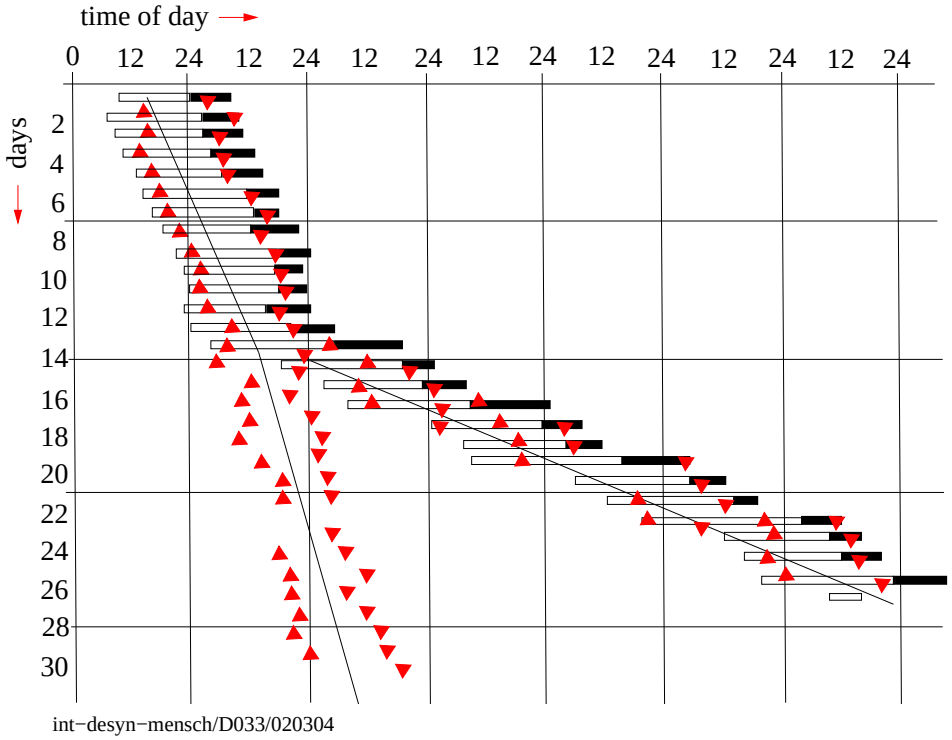

Figure 1.8: *Internal desynchronisation of body temperature- and sleep-wake-rhythm in humans under conditions without time cues in a subterranean appartment: In the first fourteen days the daily maxima and minima of the body temperature run parallel to the sleep-wake-cycle. The period length is 25.7 h for both processes. Afterward the body temperature rhythm shortens somewhat (period length 25.2 h) and the period of the sleep-wake-rhythm lengthens considerably to 33.4 h. To see the time course better, not only the days are plotted beneath each other, but additionally seven days next to each other. Therefore the values and curves should show up seven times next to each other. This would have blurred, however, the diagram and was therefore not done. After Wever (1979)*

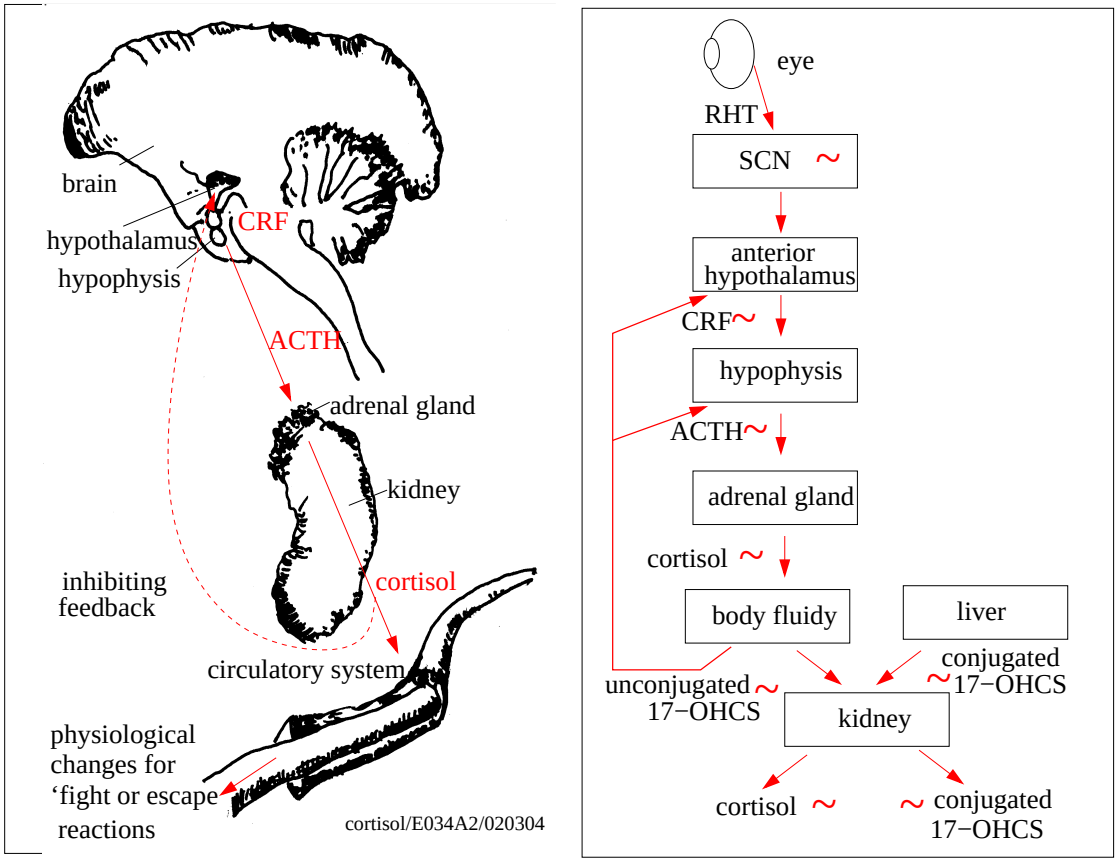

Figure 1.9: *Control of the daily cortisol secretion via the hypothalamus-hypophysis-adrenal-axis. The light-dark-cyle is perceived via the retina of the eyes. Signals are conducted to the SCN and synchronize the circadian rhythm of its pacemakers. SCN signals induce the posterior hypothalamus to secret cortisol-releasing factor (CRF) in a daily and ultradian way (and also directly in stress-situations). CRF causes the secretion of the adenocorticotropic hormone ACTH in the anterior lobe of the hypophysis. ACTH triggers cortisol secretion in the adrenal cortex. It reaches via the blood circulation different targets (eosinophils, plasma, air ways) and causes in stress-situations 'fight-or-flight'-reactions. By feedback cortisol inhibits the hypothalamus and the hypophysis. Cortisol and corticosteroids are metabolized in the liver and excreted via the kidney. ∼: circadian rhythm. After Moore-Ede et al. (1982)*

2 Where are the centres of rhythmic control?

Are the various daily rhythms of humans and other mammals controlled by just one or by several central clocks? To find an answer, Richter (Richter (1965), Richter (1967)) destroyed various brain regions and brain glands of rats and checked, whether the daily rhythms are still observable or are absent. In this way it was found that a centre lies in the paired suprachiasmatic nucleus (SCN) in the anterior part of the hypothalamus (figure 2.1). These findings were re-discovered by Moore and Eichler (1972) and at the same time by Stephan and Zucker (1972). For the history of the discovery and more recent results see Weaver (1998).

In all mammals the circadian system is dominated by the SCN. It is the central oscillator and controls a large number of physiological processes and rhythms in the behaviour. Examples are among others the locomotory activity, the sleep-wake-cycle, thermoregulation, torpor, hibernation, functions of the cardiovascular system and many endocrine processes. Likewise the synthesis and secretion of the melatonin is controlled by the SCN.

A further important indication of the role of the SCN as a main oscillator were recordings of a rhythmic electric activity in the SCN. This rhythm was still observable in the SCN, even after it had been isolated from the surrounding tissue by lesions. In the surrounding tissue, however, the rhythm was lost after the lesion (figure 2.2 and Inouye and Kawamura (1979)). This proved, that the SCN is an autonomic rhythm-generator and that it transferred the rhythm to other structures via nervous connections.

The metabolism in the SCN is also rhythmic (Schwartz and Gainer (1977)). During the day it is high, during the night low (figure 2.3). This rhythm is observanle also in the isolated SCN in vitro (Newman and Hospod (1986)). This has been shown by using 500 μm thick hypothalamic sections (Green and Gilette (1982); Groos and Hendricks (1982); Shibata et al. (1982)). The firing of indicidual neurons can be observed up to three days under constant conditions, if the medium and the temperature has been chosen correctly (Prosser and Gillette (1989), figure 2.4).

Syrian hamsters, the SCN of which were removed and which became thus arhythmic, show a circadian rhythm in behaviour, if fetal SCN tissue is implanted (Lehman et al. (1987) and figure 2.5 for rats). The tissue can also be obtained from other species (Syrian hamster, mice or rats). The induced period length corresponds to that of the donor (Syrian hamster, mice) (Sollars et al. (1995)).

Cultures of SCN-cells can induce even after weeks a circadian rhythm in Syrian hamsters, the paired SCN of which was destroyed. The cutured cells were implanted at the place of the brain, at which the SCN is normally located (Silver et al. (1990)). Thus the *structure* of the SCN does not need to be preserved. If the SCN-cells of

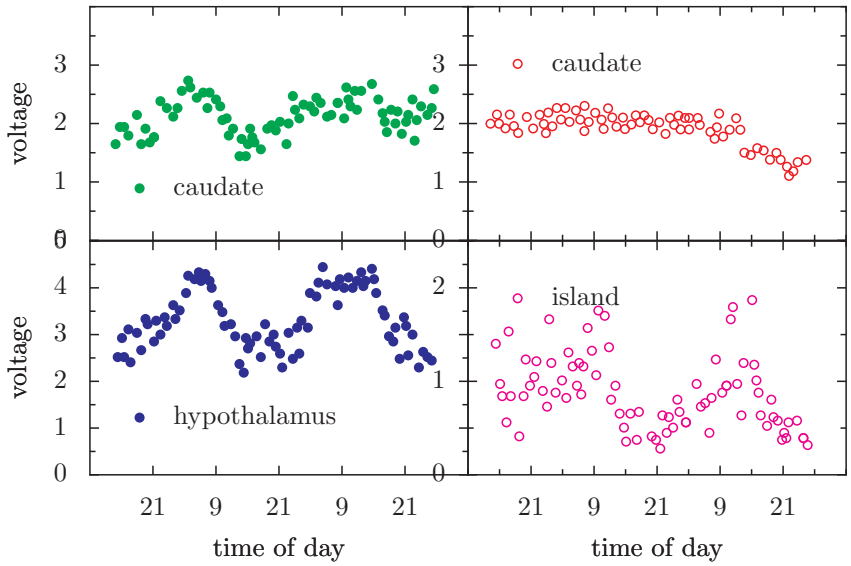

Figure 2.2: *Isolation of the SCN from the neighboring tissue by a ring-like cut hamstrings the daily electrical activity outside the SCN (compare left upper part, before the isolation of the SCN, with the right upper part, after the isolation). The daily rhythm of electric activity in the SCN, however, is still existent (compare left and right bottom part, in both cases a circadian rhythm is still present. After Inouye and Kawamura (1979)*

two genotypes with different periods are implanted together, a coherent rhythm is found. This shows, that the cells are able to communicate with each other and that they arrange about an average period length. Transgenic cells with markers can be used to label the responsible cells (Ralph et al. (1993)).

Interesting recent studies are by Welsh et al. (1995). At individual, dissociated SCN-neurons the electrical activities were recorded with multi-micro-electrode plates for longer periods. In one culture cells with various phases and periods were found, although functional synapsis existed (figure 2.6).

2.1 Pacemaker cells in the suprachiasmatic nucleus

What are the pacemaker cells in the SCN? Do different functional parts exist in the SCN? The SCN of mammals consists of 8000 to 10 000 neurons. Seen in a *vertical* section they form a nucleus and a shell with characteristic neurotransmitters of the neurons, with different innervations (overview Moore (1997), Esseveldt et al. (2000), figure 2.7) and probably also with different functions: The oscillators in the cells of the nucleus seem to react to the signals of the retina caused by light, whereas the oscillator cells of the shell do not. However, the oscillators of the nucleus and the shell are coupled mutually and possess therefore the same phase relationship. The electrophysiological activity of *horizontally*

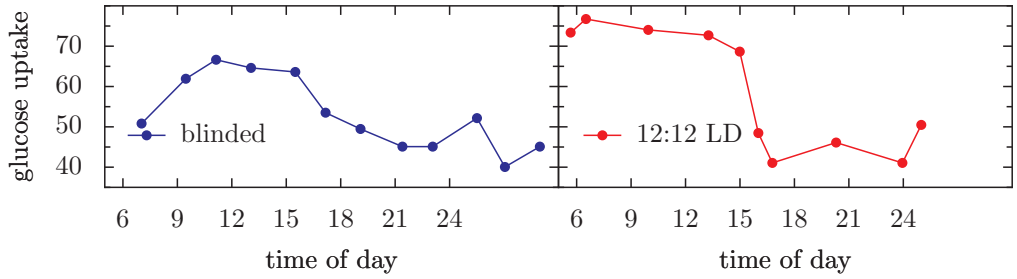

Figure 2.3: *The metabolism in the SCN has a circadian time course, as shown by the accumulation of the glucose-analogon 2-deoxi-D-glucose (this analogon is in contrast to glucose not metabolised). During the day phase the concentration in the SCN is high, during the night phase low. Each point is the result of a measurement in one animal, which had been killed at this particular time. The right curve is from animals with intact eyes in LD cycles, the left curve from blinded animals (both in physiological darkness). In both cases differences are found in the glucose uptake between the day- and the night phase. After Schwartz et al. (1979)*

sectioned SCN disks of Syrian hamsters show two specific oscillating components (Jagota et al. (2000)). They could reflect the activity of a *morning-* and an *evening-oscillator*, which had been concluded already before from behavioural studies (Pittendrigh and Daan (1976), Illnerova and Vanecek (1982)). Photoperiodic reactions were supposed to come about by the interaction of a morning- and an evening-oscillator. Long and short photoperiods do indeed influence the maxima of the morning- and evening-components of electric recordings differently (Jagota et al. (2000)).

Retinal informations are transducted via the retinohypothalamic tract (RHT, figure 4.3) and additional pathes to the intergeniculate leaf (IGL) via the geniculohypothalamic tract (GHT) to the ventrolateral part (*shell*) of the SCN. This part contains neurons, the activity of which is under circadian control. The rhythms are light-dependent. The dorsomediale part (*core*), however, receives inputs from non-visual sources and the neurons exhibit therefore rhythms, which are light-independent (references in Ibata et al. (1999)). The fire rate of the neurons shows a circadian rhythm. High fire rates during the subjective day seem to correlate with peptides and with the neurotransmitter gamma-amino-butyric acid (GABA) and to utilize normal synaptic interactions. Rhythmic informations could, however, also be transferred by diffussible substances.

If the SCN is destroyed, other rhythms are still found such as the wie das anticipatory food uptake-behaviour: Mice with destroyed SCNs continue to show this behaviour. They must therefore be controlled by a further pacemaker centre. Cell populations in various areas of the hypothalamus seem to be responsible for it (Marchant and Mistlberger (1997), Boulos and Terman (1980)). Whether the circadian rhythm of the REM sleep is also controlled by the SCN is debated (Stephan and Nunez (1977); Mouret et al. (1978); Yamaoka (1978)). It was already mentioned,

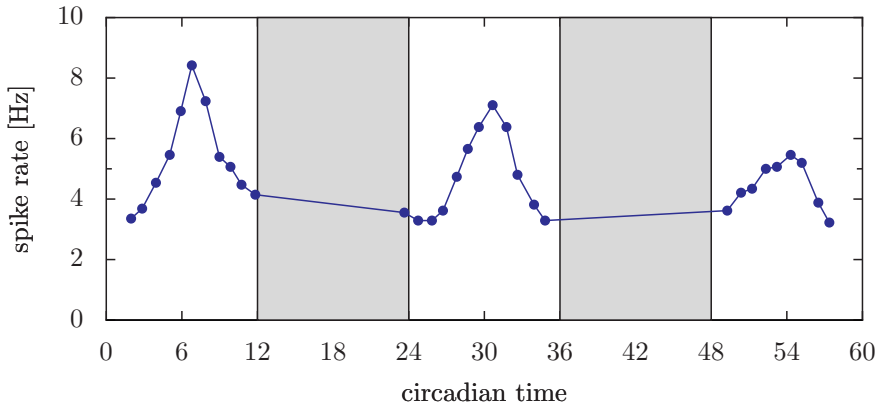

Figure 2.4: *Electrical activity in the SCN neurons (firing rate (Hz)) in vitro during three circadian cycles (circadian time, x-axis). Mean values of 4 (first cycle, 8 (second cycle) and 3 records. Grey: Subjectiv night. After Prosser and Gillette (1989)*

that the retina contains a circadian oscillator. Potentially there is also an enteric oscillator. Whether all these oscillators use the same clock mechanism has to be clarified. For an overview article see Rosenwasser and Adler (1986).

The control of the body temperature occurs mainly in the preoptic area (POG) and in the anterior hypothalamus (POAH) (Berner et al. (1999), Hori et al. (1999)). The POAH is temperature-sensitive and an integrating centre (Saarela and Reiter (1994)). Lesions in this area disturb the temperature-control. The temperature of the environment influences also control of the body temperature. Furthermore the behaviour affects the temperature control. Bilateral POAH removal in rats shifts the mean temperature from 37.0 to 38.6^0C. The circadian rhythm of the body temperature is, however, still found and the amplitude of the rhythm even increased by a factor of three. The surgery has thus affected the temperature control, but not the circadian rhythm of the temperature control.

The circadian control of temperature occurs in the SCN of the hypothalamus, as shown by a number of assured evidences which will be presented later. Thus, the circadian rhythm of body temperature (and of activity), disappears after eliminating the suprachiasmatic nuclei (figure 2.8, Moore and Eichler (1972) and Stephan and Zucker (1972)). The mean temperature however is kept, that is, the homeostatic control of body temperature is still working.

Special strains which differ in various circadian parameters connected with building nests contain various degrees of AVP-immunoreactive neurons in the SCN (Bult et al. (1993)). In a light-dark-cycle the number and volume of vasopressin-containing cells fluctuated with a circadian and an annual period (Hofman and Swaab (1993)).

How the oscillators in the SCN control the locomotory activity and other events in a circadian way is poorly understood so far. Figure 2.10 shows, how a target cell of the SCN receives via reactions in the cytoplasm as well as in the nucleus neuronal signals under circadian control. Neuropeptid Y as well as serotonin are supposed to be involved in the signal transduction by afferent neurons of the SCN (Marchant and

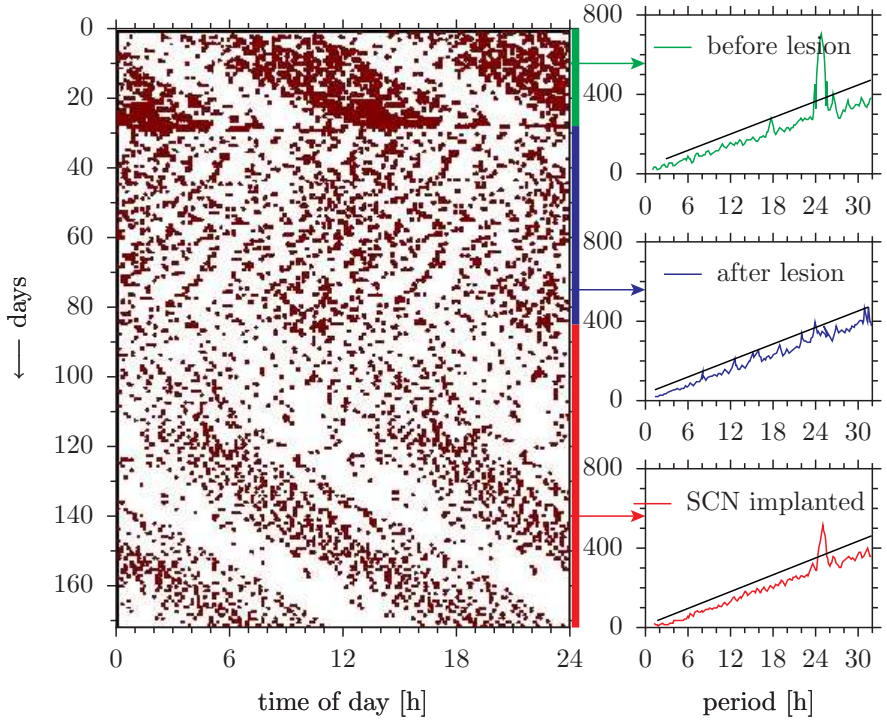

Figure 2.5: *The SCN of a rat was removed on the 28th day of freerun (running wheel activity). The rhythm disappeared, as shown in the actogram (left). If fetal SCN tissue is implanted (85th day,* trans*), a circadian rhythm of locomotor activity reappears. At the right the power spektra for the pre-lesion period (top), the post-lesion time (center) and the post-transplantation period (bottom) are shown. The 25 h rhythm, which is significant before the lesion (green maximum above the significance threshold), disappears (blue curve) and reappears again after neonatal SCN was implanted (red curve). After Wollnik (1995)*

Mistlberger (1997)). If neuropeptid Y is offered systemically, the circadian rhythm of locomotory activity of mice is influenced (Lach and Srebro (1995)). The figure shows also the transfer of the light signals from the retinular ganglia cells in the eye via the retinohypothalamic tract. Details in the legend.

What are the target organs of the efferent signals of the SCN? From the various outputs of the SCN up to now only the projection to the pineal are completely known. How other effector tissue receives the informations from the SCN is only partly known. Is the information transferred only by neurons? Is the information coded in form of pulses?

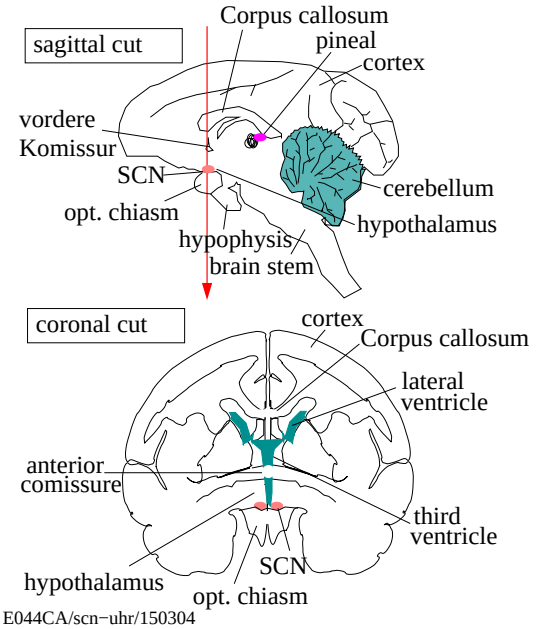

Figure 2.1: *Anatomy of the squirrel monkey brain in a sagittal (top) and a coronal section (bottom; the res arrow indicates the plane of the section). The paired suprachiasmatic nucleus (SCN) lies lateral to the anterior tip of the third ventricle above the optic chiasm. After Moore-Ede et al. (1982)*

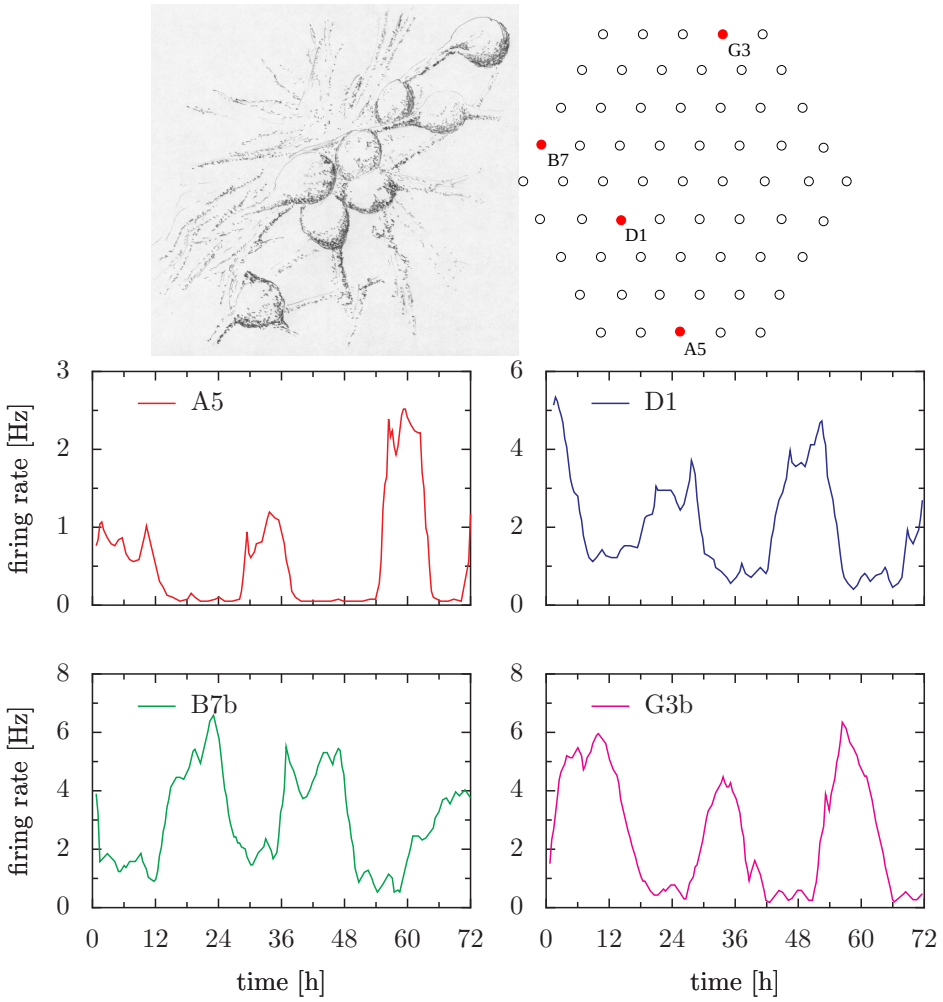

Figure 2.6: *Firing rate of individual SCN neurons, which were separated (top left). From four of them the electric potential was recorded for 72 h with a multi-micro-electrode plate (top right, A5, D1, B7b, G3b). The electrical activity (firing rate, y-axis) of the four cells A5 (red curve), D1 (blue curve), B7b (green curve) and G3b (magenda) is shown in the lower part of the figure. Note, that the cells exhibit different phases and periods, although functional synapsis are present. After Welsh et al. (1995)*

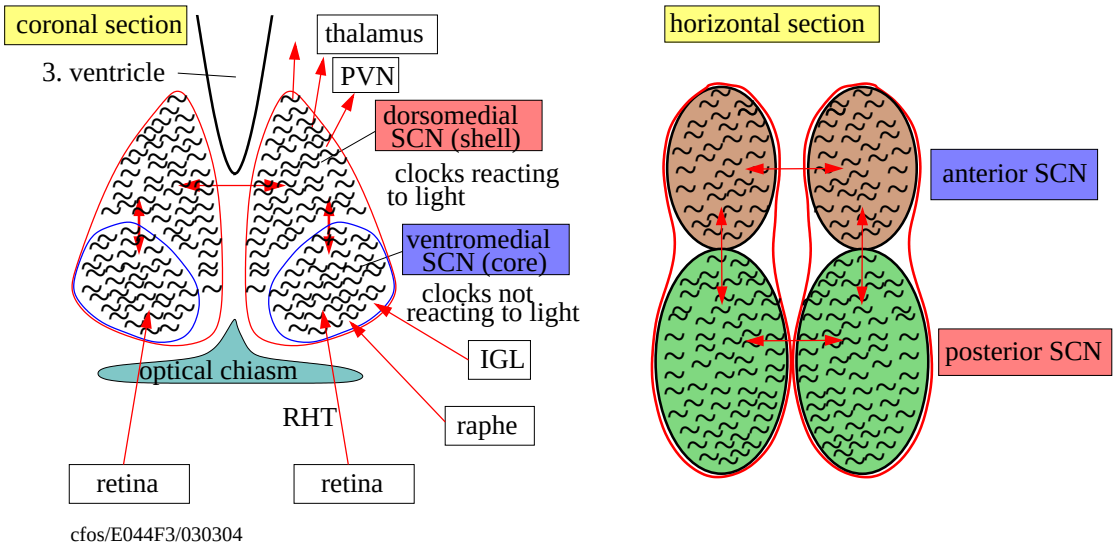

Figure 2.7: *Left: The suprachiasmatic nuclei (SCN) of mammals are paired structures at the lower tip of the third ventricle and above (‘supra´) the optic chiasm in the hypothalamus. A coronalal section through the SCN exhibits a dorsomedial part (‘shell´) d and a ventrolateral part (‘core´). Inputs come from the retina via the retinohypothalamic tract (RHT), the raphe nucleus and the intergeniculate leaf (IGL). Outputs protract to the thalamus, the paraventricular nucleus (PVN) and other areas of the brain. The shell is supposed to consist of numerous cellular oscillators, which do not react to light inputs. The core on the other hand consists of cellular oscillators, which react to light signals. Right: A horizontal section shows the anterior SCN (brown), which consists of a population of cells representing the morning-oscillators, and of the posterior SCN (green), representing the evening oscillators. Coupling between the various groups is indicated by the double arrows. After Shigeyoshi et al. (1997), Inouye et al. (1993) and Dunlap (2000)*

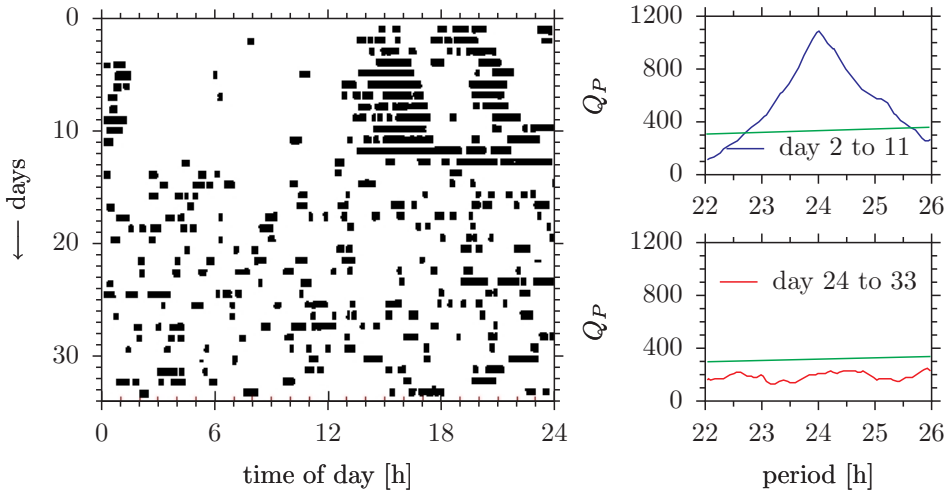

Figure 2.8: *The circadian rhythm* of body temperature *of a Syrian hamsters dissappears, if the suprachiasmatic nuclei are distroyed (on the elevens day). Periodogram for day 2 to 11 at the top right before the elimination of the SCN, for day 24 to 33 below after elimination of the SCN. After Refinetti et al. (1994)*

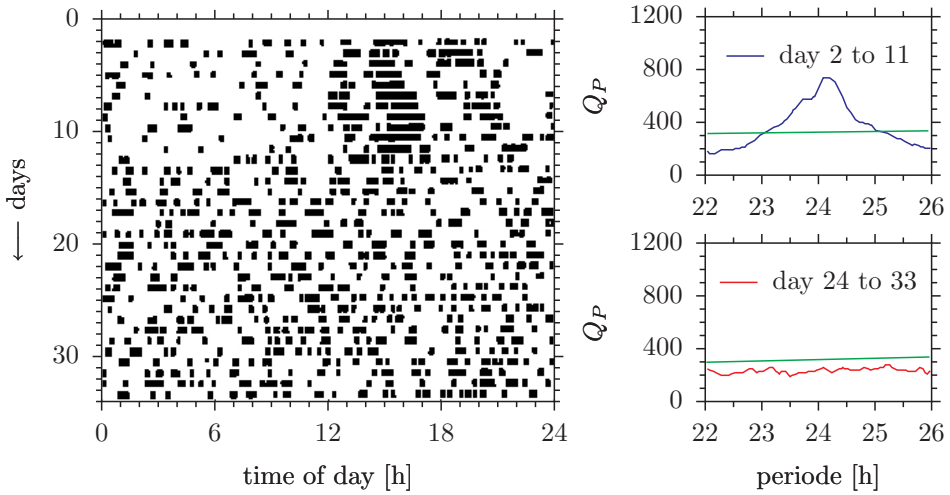

Figure 2.9: *The circadian rhythm of locomotory activity of a Syrian Hamster disappears after the suprachiasmatic nuclei were distroyed (at the elevens day). Periodograms for day 2 to 11 top right, for day 24 to 33 below. After Refinetti et al. (1994)*

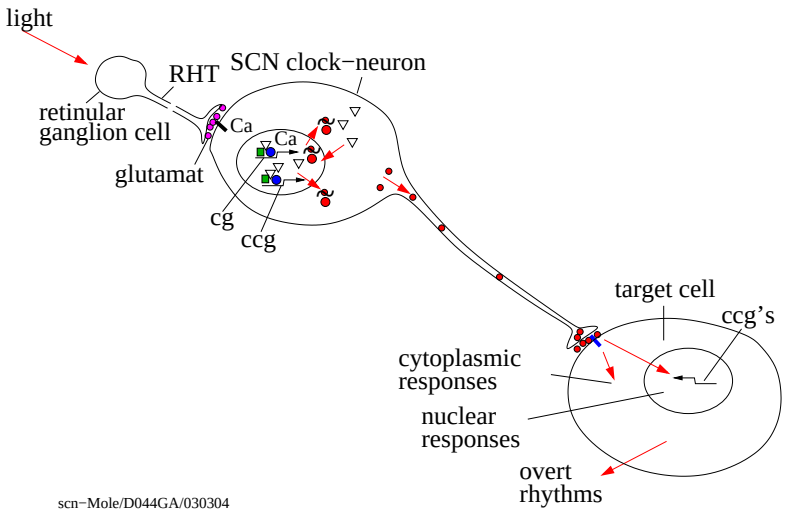

Figure 2.10: *Events between light reception, SCN clock neurons and target cell: Light is received in ganglion cells of the retina. Neurotransmitter glutamate (violet) is emitted and reacts with receptors (black rectangular). The expression of mPer and mCry of the clock-gen (cg) is induced via a negative feedback loop with amplifying factors CLOCK (green) and BMAL (blue).* Ca^{2+} *is also involved. The clock-proteine-mRNA (red circles with ~) is produced, leaves the nucleus and synthetizes the clock-proteine (triangle) in the cytoplasm. It reaches the nucleus, interacts with mPER and facilitates its translation by inhibiting CLOCK-(green) and BMAL-(blue) depending transcription: As a result the mRNA concentration decreases. With a time delay the negatively acting complexes are inactivated and the gene expression starts anew. The next round of negative and positive acting factors boosts the rhythmic expression of the clock-controlled genes (ccg´s). The products, clock-controlled proteins, inform the SCN-neurons about the time of day and the signal is via synaptic or paracrine signals passed to the target cells. Target-specific circadian outputs via cytoplasmic or nuclear reactions influence secondary ccg´s. N-acetyl transferase is an example. It controls melatonin synthesis. After Hastings and Maywood (2000)*

3 How do internal clocks work? Experiments with rodents

One of the main aims of chronobiologists is, to decode the function of day clocks. For this purpose they study for instance mutants, the clocks of which differ from the one of the wild type by running faster, slower or not at all. Using molecular biological methods the involved genes and their interactions can be found out. A (simplified) molecular model of the circadian clock of mammals is shown in figure 3.1. It consists of several clock-genes, which inhibit via feedback, time delay and interactions with transcription factors their own expression. Light synchronizes the oscillator sending signal to the clock-genes after having been absorbed by photoreceptors.

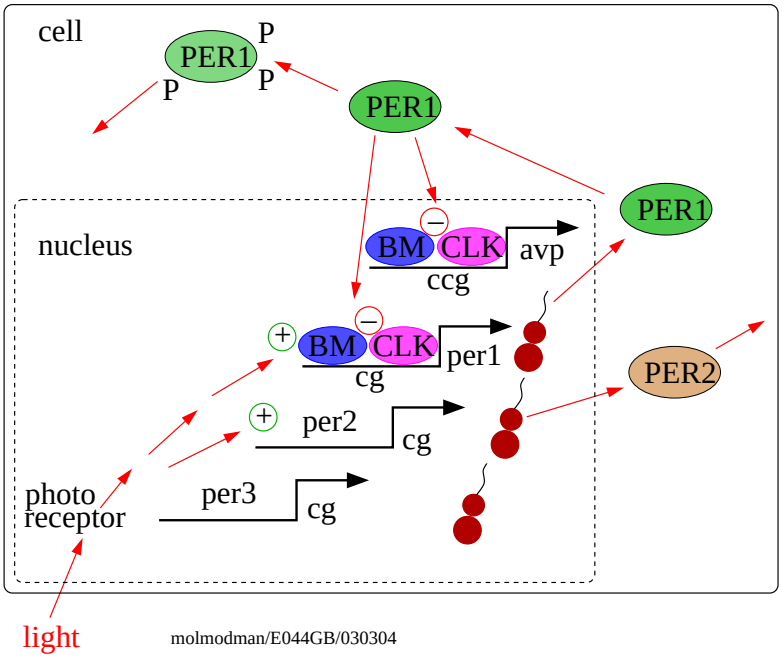

Figure 3.1: *Molecular model of the circadian clock of mammals: Clock-gene mper1, mper2 and other genes (not shown) inhibit time delayed and by interacting with transcription factors BMAL (BM) and CLK their own expression (per1, per2 and per3 are clock-genes cg = clock gene, brown: mRNA). PER is degraded by phosphorylation (P, bright green). Light synchronizes the oscillator by sending a signal to the clock-genes, after having been absorbed by photoreceptors. PER1 inhibits also the clock controlled genes (ccg) such as the avp-gene, which expresses AVP. Nucleus dotted, cell solid box. After King and Takahashi (2000), Dunlap (1998) and Reppert and Weaver (2000)*

4 How are daily rhythms synchronized by the 24 hour day?

A clock can be precise only, if it runs either very accurate (as for instance a quarz clock or a atomic clock), or if it is set daily. Since biological clocks are not precise enough or do for other reasons not run with exactly 24 h, they have to be synchronisiert with the environmental day. How is this done?

In most organisms the circadian clocks are synchronized by the light-dark-cycle of the day. This is, however, not a simple affair (that, for instance the transition from darkness to light in the morning sets the clock in a certain phase position). This would already not work, because the begin of the light period shifts during the course of a year. In the summer the light period would start earlier as compared to the winter, especially in regions with temperate and higher latitudes. Synchronization must be more complicated. One possibility would be, if both, the onset of light as well as the onset of darkness would be used and if both informations set the clock. Another possibility would be, if there are two circadian clocks in the organism. One of the clocks would be set by the onset of light, the other one by the onset of night. Both clocks could interact with each other and lead to a common time which is used by the organism. This kind of mechanism would have the additional advantage, that the organism gets informations about the season. How this is done in the various organisms is not yet known. It is known, however, how light is perceived by which receptors in the eye, how signals are transferred to certain centres in the brain and how circadian clocks which are located there, are synchronized. This will be the content of the following.

4.1 Eyes synchronize the day clock of mammals

Whereas in other vertebrates extraretinal photoreceptors are involved besides the eyes in synchronizing the day clocks with the external day, in mammals only the light perceived by the retina of the eyes is able to do that (4.1). As you know, the rods and cones are responsible for vision, but a population of retinal ganglia cells is able to recognize, whether light or darkness prevails in the environment. These bipolar cells, known as the Landolts clubs, are located in the outer nuclear layer and end between the pigmented epithel and the internal and external segments of the rods and cones (Locket (1999), Van Reeth et al. (1997)). They seem to be specialized for recognizing the light conditions of the environment and its temporal structure (figure 4.2). They are spread over the entire retina and project to the SCN and not to the visual centre of the brain (references in Provencio et al. (1998)). They are connected with each other either as adding or as averaging processor cells (Foster et al. (1993)).

These ganglia cells contain a retinal pho-

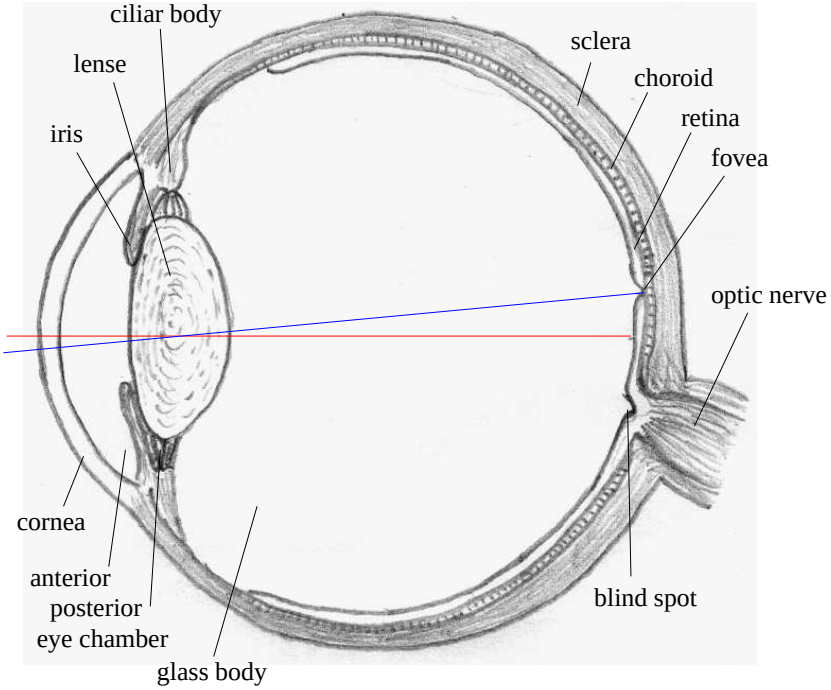

Figure 4.1: *Longitudinal section through human eye with cornea, anterior eye chamber, iris, lens, ciliar body, glass body, retina, choroid, sclera, Zentralgrube, fovea and optic nerve. Eye axis (red) and visual line (blue) are indicated. Drawn by the author after a figure in Mörike and Mergenthaler (1959)*

topigment as for instance melanopsin which was detected in fishes (Soni et al. (1998)) and amphibia but is found also in mammals (Provencio et al. (1998)). The pigments of the photoreceptors, which absorb the light used to synchronize the circadian behaviour of mammals with the light-dark-cycle are opsines with cis-retinaldehyde as a chromophore[1].

[1]The trans-isomerisation of the 11-cis isomers of vitamin A-aldehyde is the first step of light transfer in all visual systems of animals

4.2 Path of the light signal from the retina to the central circadian clock, the SCN

To synchronize the circadian clocks of mammals, light is perceived by the just mentioned bipolar ganglia cells in the retina. They project via a special path, the retinohypotalamic tract (RHT), to the SCN (figure 4.3). The two other nerve tracks from the eye to the brain, the optic nerve and the accessory optic system, do not influence synchronization. The retinohypothalamc tract was found by using autoradiographic methods (Moore and Lenn (1972)).

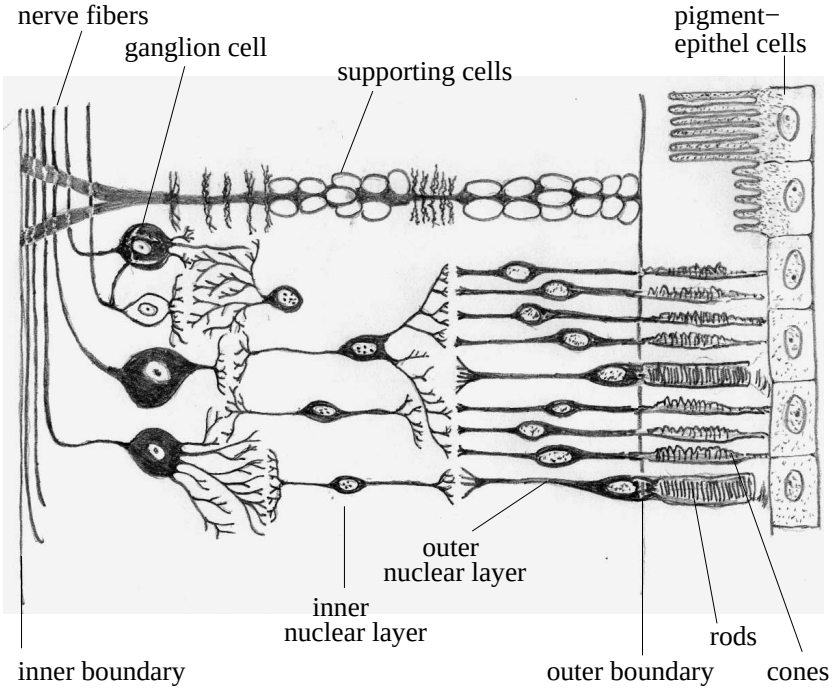

Figure 4.2: *Close-up of retina with stack of several neuronal layers. Light (from the left) passes these layers and hits the photoreceptors at the right consisting of rods and cones. Chemical transformations mediate a propagation of signals to the bipolar (outer granular layer) and the horizontal cells (inner granular layer). The signal is then propagated to the amacrine and ganglion cells. These neurons may produce action potentials on their axons. Some of the ganglion cells (light cell) are specialized for perceiving the light/dark environment. Drawn by the author after a figure in Mörike and Mergenthaler (1959)*

Neural signals (glutamate as neurotransmitter) reach the SCN via the RHT and synchronize the pacemaker (see figure 2.10).

4.3 Other time cues for synchronizing the day clock

Not only light, but also the activity of the animals synchronize their circadian rhythm. If a running wheel is offered to the animals for two hours per day, the rhythm of the animals has under otherwise constant conditions a period length of exactly 24 h. It is thus synchronized. The locomotory activity increases the serotonin content in the SCN. Serotonin-agonists shift the phase of the circadian clock in the same way as locomotory activity does. It might therefore well be, that serotonergic afferences are part of the activity-dependent synchronisation mechanism (Edgar et al. (1991a), Edgar et al. (1991b), Edgar and Dement (1991)).

The circadian rhythm can be synchronized also, if feeding is restricted to a certain time of the day or if the animals are stressed with electric stimuli (Nagai and Nakagawa (1992)). Sociale signals are also

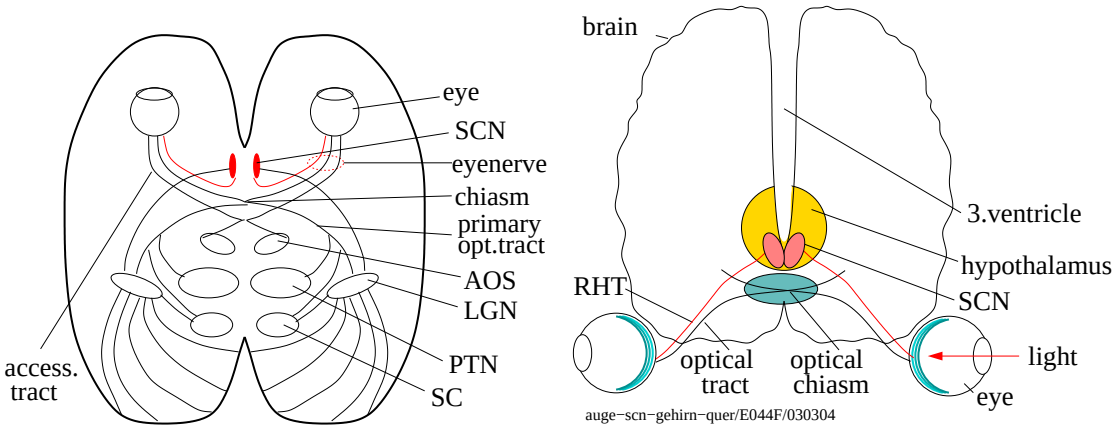

Figure 4.3: *Visual paths from the eye to the brain in the hamster. Left: Brain from above. Right: Cross section through brain in the area of the hypothalamus and the SCN. Light is perceived by the retina of the eyes and the signals transferred to the primary optic tract, the accessory optical system (not shown) and the retinohypothalamic tract (RHT) to the visual cortex in the brain. The RHT terminates in the suprachiasmatic nucleus (SCN), which contains numerous pacemaker cells for the circadian rhythmicity. After Moore-Ede et al. (1982)*

time cues.

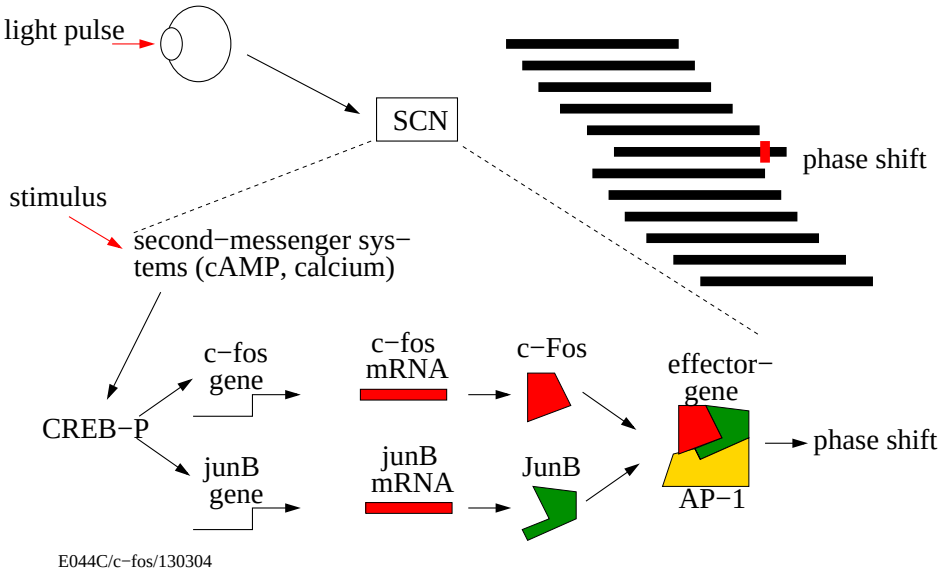

Figure 4.4: *Top: Light pulses are perceived by the retina of the eyes and transferred as signals to the SCN. There the phase of the circadian oscillators is shifted and as a result of it also the locomotor activity rhythm (black horizontal lines for each day, red marking: Time of light pulse, which advances the rhythm). Below: Signal transducing cascade for synchronizing hamsters by light-dark-cycles. An external stimulus (a neurotransmitter or a hormone) activates a second messenger system (cAMP,* Ca^{2+}*), by which cAMP response element binding proteins (CREB) are phosphorylated. This is a prerequisite for activating immediate early genes (IEGs) such as c-fos and junB. Transcription (→mRNA) and translation (→c-Fos, JunB) produce proteins of the Fos or Jun family. They form heterodimeres and combine with the AP-1 region of other gene sections. This promotes or inhibits their transcription. After Wollnik (1995)*

5 Adaptations to the seasons

Mammals of higher latitudes are exposed to the rigours of the winter and had to adapt to it. During the course of evolution numerous morphological and physiological properties were selected. An especially successful strategy is an annual rhythm, which is controlled by an internal annual clock and which allows the animals to plan ahead for the changes in the environmental conditions during the course of the year. With photoperiodic timing the annual clock can be synchronized with the seasons. Annual rhythms are known in various mammals. The golden mantled ground squirrel *Spermophilus lateralis* is an example (Pengelley and Asmundson (1974)), the squirrel *Tamiasciurus hudsonicus* (Becker (1993)), bats (Daan (1973)), sheep (annual rhythm of wool growth, (Reis (1992), rectal temperature of Corriedale-sheep under tropical conditions (Dasilva and Minomo (1995))), Resus monkeys and other mammals (see Tabelle 2.1 in Gwinner (1986)). As an example we will have alook at the annual rhythm of the Dsungarian hamster and seine synchronization mit den seasons durch photoperiodice processes ansehen.

5.1 Adaptations of the Dsungarian hamster for the winter

The dwarf hamster *Phodopus sungorus* and *Phodopus campbelli* are often mixed up by calling both 'Sibirian hamster' or 'Djungarian Hamster' (figure 5.3). They differ, however, considerably (Ebling (1994)).

In the fall the Dsungarian hamster is put in the right mood for the winter by the shortdays. The body weight decreases, the gonads regress, the fur becomes white and dense[1], torpor occurs in which the body temperature is lowered temporarily to low temperatures. After some time under shortday regression comes to a halt and the gonads begin to develop again, the body weight increases and the summer fur is formed (figure 5.3). This '*recrudescence*' begins already under shortday (figure 5.1). It is thus not a photoperiodic reaction, but (probably) controlled by an endogenous annual rhythm. It occurs in males and females (Lerchl and Schlatt (1993)).

The photoperiodic informations are transferred by melatonin secretion of the pineal. The melatonin-producing neuronal net contains an effective light-memory (Lerchl (1995)).

5.2 Torpor and its physiology

Small hamsters are able to direct the energy balance during unfavourable times by a special state called torpor. During torpor the energy consumption is reduced (Berger (1988), Berger (1993)). Environmental temperature and food supply are important factors for the induction of torpor. In this way the animals are able to react more flexible to environmental conditions

[1] It isolates better than the brown summer fur and has at low wind speeds a higher heat resistance (Walsberg (1991)).

and unpredictable weather changes (Ruf et al. (1993), Ruf and Heldmaier (1992)). The main factor for the occurance of torpor is however shortday.

Torpor in the Dsungarian hamster is also photoperiodically controlled. Under shortday and at lower external temperatures the body temperature is lowered for 5.4 h per day as a mean (0.3 to 9.4h) to $14-31^0$C (figure 5.1)[2]. The energy consumption is reduced considerably during torpor. This allows the animals to search for food in the sibirian steppe even in the winter without spending more energy as they would by staying all day in the burrow (Ruf and Heldmaier (1992)).

The longer the animals stayed under shortday, the more frequent torpor occurred. After 130 shortdays a maximum of occurrence of torpor was observed. Male animals showed by the way more frequently torpor as compared to females. A circadian rhythm controls the time at which torpor occurs and the day-night-cycle synchronizes the torpor rhythm. During darkness the occurrance of torpor increases (Kirsch et al. (1991)). Torpor occurs under shortday conditions only if the testes are regressed. If testosteron in injected during shortday, the torpor is completely prevented. The annual timing process which controls the torpor, is however unaffected. In castrated animals the torpor finishes later (Ouarour et al. (1991)). Castration between the first week before and the fourth week after onset of shortday promotes the occurrance of torpor (Ouarour et al. (1995)).

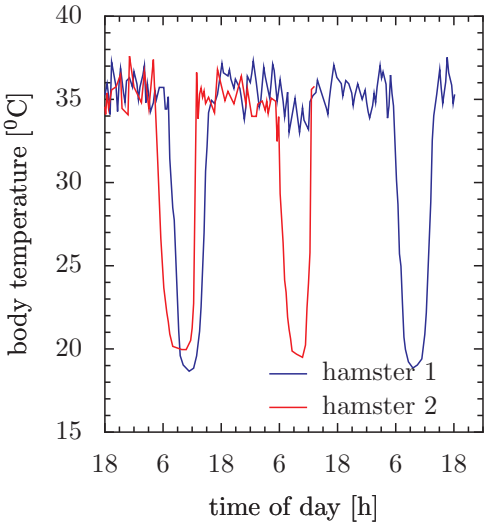

Figure 5.1: *Torpor in two Djungarian hamsters. Body temperature of hamster 1 (red curve) measured for two, and of hamster 2 (blue curve) for 3 days. Both hamsters in winter fur, hamster 1 from January 18 to January 20, hamster 2 from November 14. to 17. Cold store with 6^0C environmental temperature with 80 lux light from 6-18 o'clock and 0.2 lux light at the remaining time. The animals became lethargic (torpor) in the early morning and lowered their body temperature for a few hours per day to $18-20^0C$ (hamster 2 on the second day only a few degrees). After Figala et al. (1973)*

Sleep, torpor and hibernation have been regarded so far as homologous processes. In the Dsungarian hamster, however, the slow-wave activity (with a power density of the EEG at 0.75-4.0 Hz) is increased after torpor. The same occurs after sleep deprivation. Thus during torpor the animal is sleep deprived. After the torpor this deprivation has to be counterbalanced by an slow-wave activity (Deboer and To-

[2] Already a single longday reduces the melatonin secretion permanently. Apparently the circadian oscillator is programmed anew ('restart') by this treatment. It has thus a long term effect. Melatonin application prevents this effect (Finley et al. (1995)). During true hibernation, however, the body temperatur can drop to almost 0^0C (Barnes (1989)).

bler (2000)). There exist further differences (Ouarour et al. (1995)).

5.3 In nature exist always exceptions

The photoperiodic control of processes in hamsters shows several exceptions. First of all, the adaptation for the winter varies quite a bit in the species (Ruf et al. (1993)). Normally Djungarian hamsters react with a number physiological and behavioural changes to shortday, as mentioned already. But not all animals react in the same way to the photoperiod and in some animals it is missing completely. It is suspected (Kliman and Lynch (1992)), that the circadian system is responsible for photoperiodic reactions, but additionally another system (reduced sensitivity for melatonin, Horton and Yellon (2001)), the strength of which varies genetically.

Gorman and Zucker (1997) showed, that the photoperiodic pre-history is important for reproductive regression. 92% of the animals kept in extreme longdays of 18:6 h light-dark-cycles do not form back their gonads completely, whereas only 10% of the animals kept in 14:10 h did so and none of the animals kept under shortdays of 10:14 h.

5.4 Photoperiodice timing, models

To adapt behaviour and physiology to the seasonal changes, the animals must receive signals from the environment, which inform them about the season. The most reliable 'time cues' is the length of the daily light period (or dark periode), which varies regularly during the course of the year. These changes are more pronounced at higher latitudes, whereas they are much smaller in latitudes close to the equator. Somehow the length of the day respectively night must be determined. If a certain length (for instance of the night) has been reached, a signal is produced which tells the animal to start the photoperiodic reaction.

We have seen already, that an internal annual clock is also able to remind an animal of the season. But even in this case the annual rhythm has to be synchronized to the season: Since the annual clocks like almost all biological clocks do not run very precisely, they would soon be out of synchrony with the season. As in most other cases, here too the photoperiodic situation in the environment is the reference.

Photoreceptors and a photoperiodic timing system are thus required. The latter could work like an hour glass: For instance the length of the night would induce reproduction photoperiodically, if a critical length is reached or erreicht or exceeded. It turned out, however, that in most cases a circadian clock measures the length of the night.

Several models have been proposed, to explain the mechanism of photoperiodic timing. An *external coincidence model* would be worth considering. In this case the circadian oscillator has to get light at a certain phase and darkness at other phases to allow photoperiodic induction. However, an *internal coincidence model* consisting of two oscillators might also be the basis of the photoperiodic timing system. In this case the oscillators are affected independently by two different external time cues, which depend on daylength[3]. In more and more cases studied so far it has been found that the circadian system consists of two oscillators (Boulos and Rusak (1982), Illnerova

[3] for instance the onset of light could be one of the time cues, and onset of night the second time cue

(1991), see also more recent results on the SCN with morning- and evening oscillators by Jagota et al. (2000)). The photoperiodic reactions of the Djungarian hamster could be explained by an external as well as by an internal coincidence model (see Goldman (2001a)). An internes coincidence model seems, however, to be the more adequate one, as experiments show (see Illnerova (1991), Oster et al. (2002), Boulos and Rusak (1982), Goldman (2001b), Puchalski and Lynch (1994)).

5.5 Photoperiodic centres, perception and transfer of the photoperiodic signals

The photoperiodice reactions are well studiedin hamsters. We should, however, also know, where the environmental signals (daylength or nightlength or both) are perceived and transferred to the centre, which serves as a 'clock for all seasons´ (Pittendrigh and Daan (1976))? Where in mammals is this centre localized and how are the photoperiodic reactions realized? Is it the same centre, which controls also the circadian rhythms, namely the SCN? This is indeed the case (overview by Schwartz et al. (2001)). If the SCN is destroyed, no photoperiodic reactions are found. In the case of the tau-mutant of the Syrian hamster with a circadian period of 20 h the photoperiodic reaction is also changed. It is, however, 'normal', if the 20-h circadian period is used as a reference (Stirland et al. (1996)).

In mammals the photoperiodic signals are perceived via the retina of the eyes. The daylength is directly transferred via the retinohypothalamic tract and indirectly via the geniculohypothalamix tract to the SCN, thus via the same pathes which are used to synchronize the circadian system in the SCN by light. After preprocessing in the SCN the information concerning daylength is transferred to the pineal. Here the photoperiodic information is converted into melatonin as the output signal. Melatonin is only secreted during the dark period. It is synthesized by NAT proportional to the length of the daily dark period and delivered to blood vessels (and perhaps or even more likely to the cerebrospinal fluid). From here it reaches the target tissues. They finally regulate the physiological and behavioural changes (Malpaux et al. (2001), Hazlerigg et al. (2001)). The neural pathes from the SCN to the pineal are shown in figure 5.2.

5.6 Projections of the photoperiodic centre

If the SCN is indeed -besides its function as pacemaker for circadian rhythms- also the centre of photoperiodic control, the pineal would be a subordinated centre, in which melatonin is produced under circadian control of the SCN and inhibited directly by light. Further elementes of the photoperiodic system are poorly understood.

Unknown is also the neuronal basis of circannual rhythms. Whereas SCN-lesions in Erdhörnchen prevent circadian rhythms as well as photoperiodic reactions, the circannual rhythm of body weight is not affected. Synchronization of annual rhythms by light and induction of hibernation are, however, influenced by SCN-lesions.

The photoperiodic situation, which is coded by melatonin, has to be decoded in melatonin receptive target areas ('melatonin readout´, Hazlerigg et al. (2001)). The pars tuberalis in the hypothalamus is one of these target areas. It contains of all target areas the highest amount of

melatonin-binding spots. The effect of melatonin on the receptor-expression and coupling via second messenger coupling was studied. In melatonin readout cAMP pathes play an important role. But cAMP-independant pathes are also involved. Presumably the expression of specific genes is changed by influencing transcription factors. In this way the function of melatonin-sensitive tissue changes. The underlying molecular processes are intensively studied (Hazlerigg et al. (2001)). Apparently the photoperiodic pre-history plays also a role which complicates the story.

Melatonin influences presumably other brain areas, thus affecting reproduction via gonadotropin secretion, gonadal activity, sexual and maternal behaviour (Malpaux et al. (2001)).

5.7 Annual rhythm of the Dsungarian hamster

In the Dsungarian hamster (*Phodopus sungorus*) the seasonal changes of environmental factors are extreme. The air temperature can rise up to 45^0C in its natural habitat during the summer and fall to -64^0C during the winter. It is therefore understandable, that the animals have to adapt physiologically, morphologically and behaviourally to the seasonal changes. Body weight, testicle weight and fur coloration (figure 5.3) fluctuate among others seasonally (figure 5.4 and Hoffmann (1978)). An annual rhythm restricts reproduction of the animals to a certain season which offers the best chances of survival for the offspring.

In the Syrian hamster (Gorman and Zucker (1997)) and the European hamster (Masson-Pevet et al. (1994)) the reproduction is also not only photoperiodically controlled, but underlies a circannual rhythm. In the Dsungarian hamster the annual component is, however, more pronounced. The photoperiod is perceived by the mother and signals are sent to the fetus (Reppert (1995)). They are responsible for the reproduction pattern of the adult animal.

The photoperiodic control as well as the annual rhythm serve to adjust the reproductive and non-reproductive periods to the season with optimal conditions for survival. An endogenous annual rhythm allone would not suffice to restrict the necessary physiological processes to the tied time of the season. An additional photoperiodic control synchronizes the endogenous annual rhythm with the annual rhythm of the environment. In this way it is accomplished, that for instance in the Dsungarian hamster all males develop sperms at the same time and that shortly afterward all females undergo estrus. This safeguards the reproduction of the animals.

5.8 Seasonal adaptations also in humans and other primates?

Since the anatomical and functional basis of the photoperiodic system of mammals is present also in primates and humans, it was obvious to check for photoperiodic reactions in these groups. Wehr (2001) give relevant informations and refer to the significance.

Seasonal reproduction is wide spread among primates. Among the Prosimians the old world and new world monkeys are shortday- and longday breeders. There are, however, also non-seasonal breeders. Seasonal breeding depends on food, the latitude and the body size. Birth occurs in most cases briefly before the time, at which

most food is available. However, photoperiodism and not food supply seems to be the proximate factor which is used by the animals for the time of giving birth (Lindburg (1987)). Rhesus monkeys are short-day breeder. The females possess a seasonal ovulation pattern, mating behaviour, conception, body weight and concentration of sexual hormones. In males body weight, fat deposition and testicle functions are also seasonally modified. This is apparently under annual control, but is synchronized by the photoperiod. Circannual cycles control also reproduction in the Squirrel monkey and die photoperiod synchronizes the rhythm to the right season.

Reproduction in humans is also affected by the season. This is shown by conzeption data, especially from those of the past (see figure 5.5 and discussion in Wehr (2001)). Women born at certain seasons show a larger variation of the time of conception in the course of the year as other women. Some individuals in the population seem to be more sensitive to seasonal effects as others (see Bronson (2004a) and the commentary of Roenneberg (2004) with an answer of Bronson (2004b)). The reproduction in humans seems to be stimulated by the lengthening of days in the spring. The average temperature, which also varies with the season, seems also to play a role. The light intensity is apparently the main main variable and the photoperiod only subordinated (Cummings (2002)).

Seasonale affective disorders SAD werementioned already (see also section chnitt 9.3). They could be connected with photoperiodic effects.

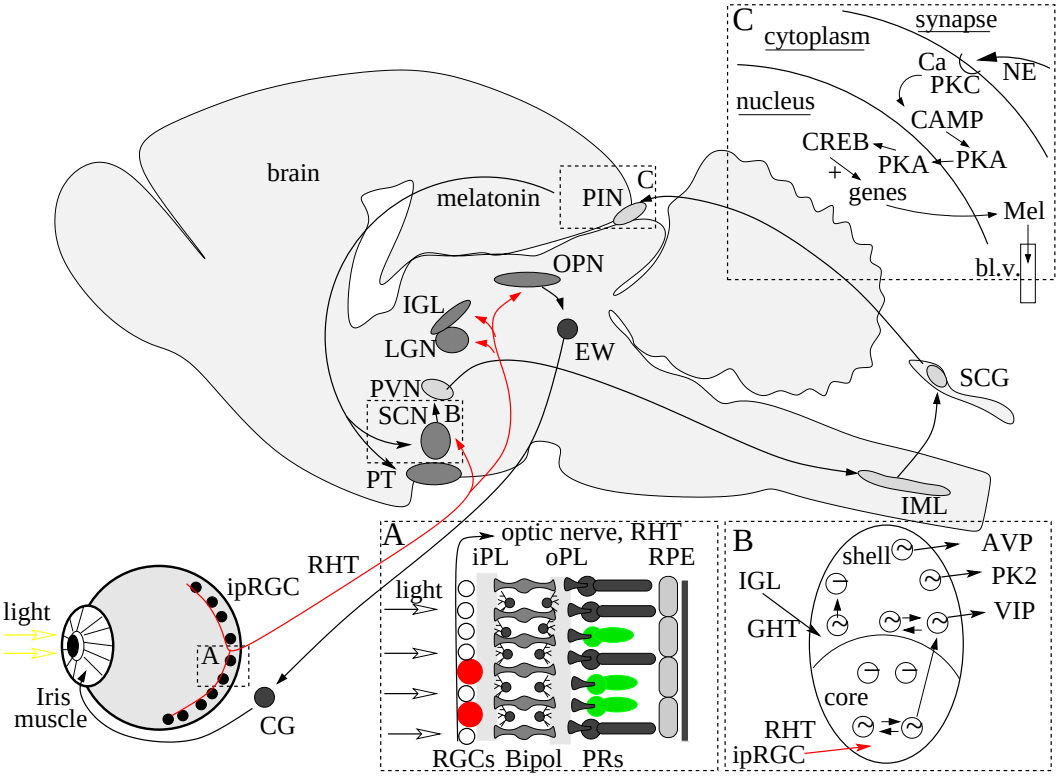

Figure 5.2: *Photoperiodic pathes in mammals: Informations concerning the daylength are perceived by the retina of the eyes and transferred by a direct path, the RHT, and an indirect path, the IGT, to the SCN. After the information concerning daylength has been ascertained in the SCN, neural signals (with GABA as neurotransmitter) are sent to the paraventricular nucleus PVN. The PVN projects via preganglionic neurons of the sympathic nervous system in the intermediolateral column (ILM) of the spinal cord (there are even two parallel projections. One might serve to synchronize the circadian rhythm in the pineal, the other, to surpress the melatonin production in the pineal). Postganglionic cells in the upper cervical ganglion (SCG) project to the pineal. After Schwartz et al. (2001)*

Figure 5.3: *Dsungarian hamster (*Phodopus sungorus*) in summer- (left) and winter fur (right). After Figala et al. (1973)*

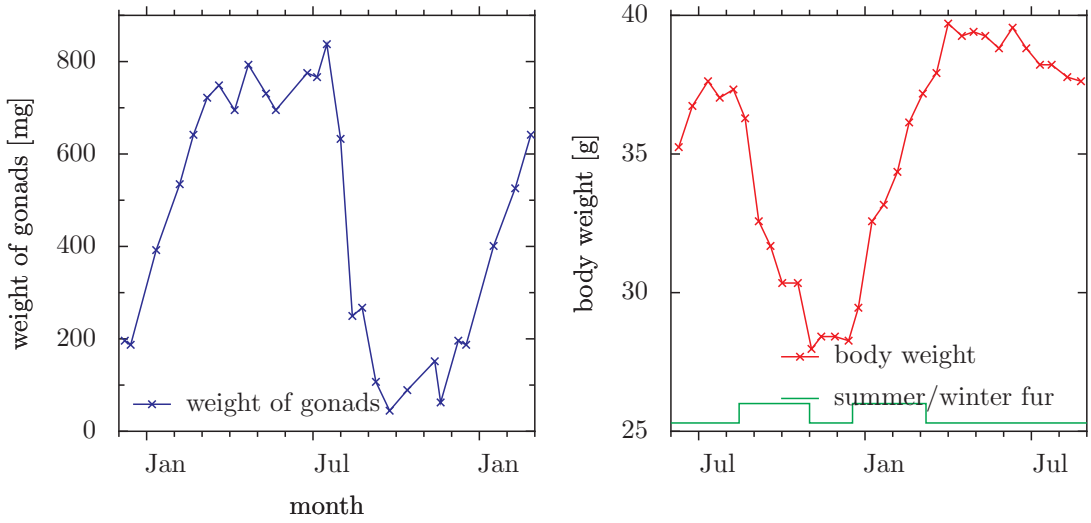

Figure 5.4: *Annual rhythm in the Dsungarian hamster* Phodopus sungorus. *In the late summer and fall body weight is reduced (red curve right) and the gonads regress (blue curve, left). After the animals have been for some time under shortdays, regression is terminated: The gonads begin to develop again, body weight increases (*recrudescence*). After Hoffmann (1978).*

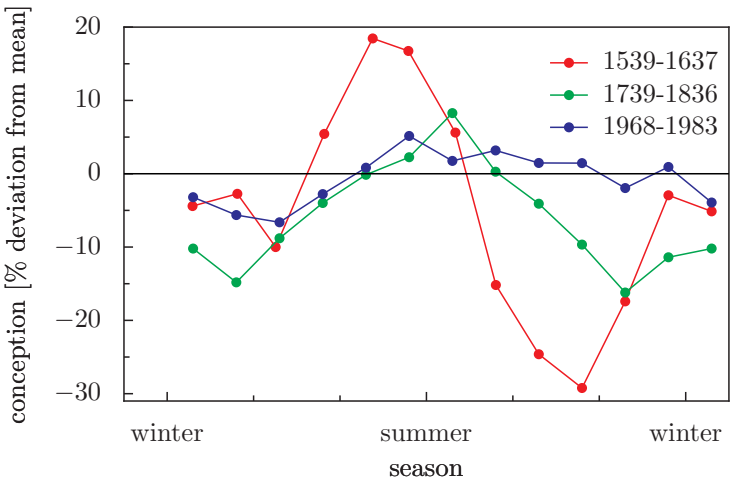

Figure 5.5: *Annual fluctuations of conception in humans during historic periods in England. Deviations from the mean. Note, that the amplitude decreases from the older (1539-1637, red) to the younger data (1968-1983, blue). The seasonal effects are much more reduced in the last period. During this period artificial illumination in the buildings took place. After Wehr (2001)*

6 Monthly rhythms also in humans?

Reproduction in humans is as in all mammals controlled in an infradian way: Estrus cycle and menstrual cycle are typical for mammals (figure 6.1).

Furthermore a circannual cycle in mammals makes sure, that the rutting season occurs at the right time of the year thus insuring that the pubs are born and brought up at favorable seasons. In man the influence of the season on reproduction is low, but established.

Menstruation is a bleeding of the uterus which lasts in woman 3 to 5 days. The uterus mucosa (endometrium) is shed. The ovarial and uterine cycle in woman is 29.5 days as an average. Since the moon cycle is 27 days (sideric) respectively 29.5 days (*'synodic´*, since the earth is moving too) it is tempting to assume a relationship between menstruation cycle and moon cycle. This is, however, not the case. Human menstruation is independent on lunar phases and days of the week (Pochobradsky (1974)). However, in monkeys of equatorial South America such relations were indeed found. The menstruation occurs at times of new moon, 14 days later at the time of full moon ovulation and conception is taking place (Erkert (1974), Erkert (1976)). Whether this offers a selective advantage or whether it is the result of social effects is unknown.

There are some indications that the menstruation cycle among woman can be synchronous. Other observations speak against it (Wilkins (1992), **?**, Jarett (1984), Trevathan et al. (1993)).

Is there also a sexual cycle in human males? It was found that the secretion activity in the auxiliary glands of males occurred parallel to the menstruation cycle of woman (Doggett and Keilers (1962)). Estrogens and 17corticosteroids in the male show an 8 to 10 day rhythm (Exley and Corker (1966)). According to Månson (1965) there is a 4 week rhythm of the leukocytes parallel to the androgen-induced nuclear appendixes in the testicles. Hornstein et al. (1964) found a 4 week rhythm of the urethra cells in the male. The growth of the beard of man fluctuates in a four- weekly rhythm (Kihlström (1971b), Kihlström (1971a)).

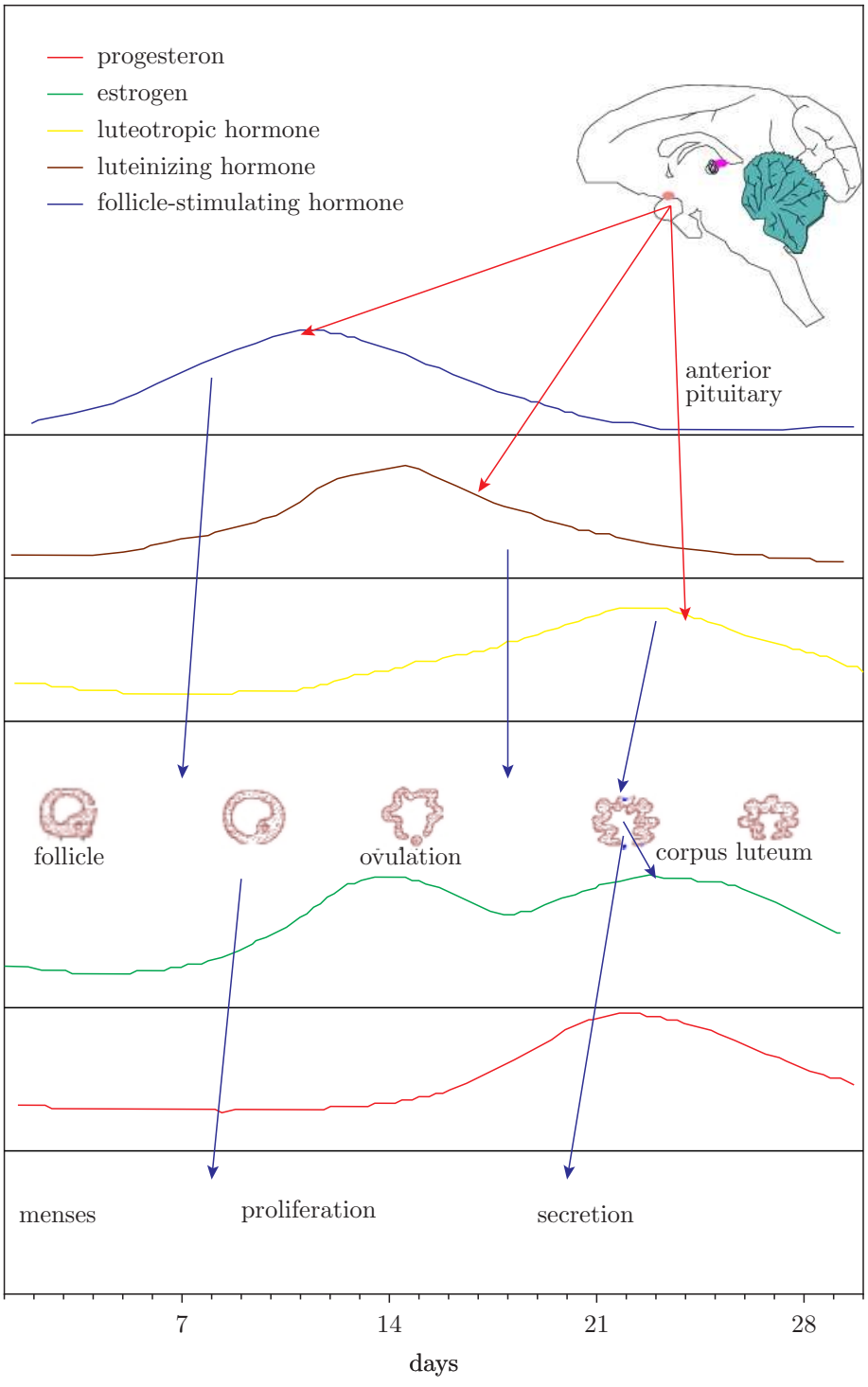

Figure 6.1: *Menstruation in women is controlled by hormons. The anterior lobe of the hypophysis (origin of red arrows) secretes the follicle-stimulating hormone. Later the luteinising hormone is secreted (second diagram) and thereafter the luteotropic hormone (third diagram). How they affect the follicle, is shown in the central part of the figure in sketches. Estrogen is secreted before and after ovulation by the follicle (fourth diagram). Together with progesterone (fifth diagram) it changes the uterus-mucosa (bottom). The stages are shown above the lower time scale (menses, proliferation, secretion). After Sommer (1990)*

7 Shift work

7.1 Why shift work?

Men were like their primate ancestors from the outset a social being. They lived in groups and it has to be expected, that some group members specialized for certain tasks. Although probably at that time most members of the group had a 'normal' sleep-wake-rhythm, but there existed already 'larks', who were awake while the rest was still asleep, and 'owls', who were awake in the night wach. This 'shift work' assured the group against attacks in the night and was safer as compared to a situation where all members of the group slept simultaneously. It was thus more advantageous for the survival of the group, if the daily activities of the group members varied in time.

Today shift work is wide spread. Reasons for it are security in police and military. Shift work is required in the social domain of medical accomodation, transportation and the supply with electricity, water and heat. Technological reasons require shift work in the chemical industry, oil industry, and steel industry. For economic reasons the working places and energy are better utilized, which reduces costs. About 20%[1] of the people in industrialized nations do shift work (Winget et al. (1978)), most of them in the industry.

[1] 27% of man, 16% of woman (Moore-Ede and Richardson (1985))

7.2 Kinds of shift work

There are different kinds of shift work:

- Boom work
- 8- or 12-h shift work
- Rotational shift work (figure 7.1, Knauth and Rutenfranz (1975))
- Permanent shift work (Rutenfranz et al. (1977)).

The most popular is the afternoon shift. Less popular is the early shift, and the most unpopular one is the night shift. Many people try to avoid shift work and prefer instead a continuous work at a shifted time. Only one third of the shift workers (among them more woman) do this on a voluntary basis. Most of them are more or less forced into it. In the middle of life the readiness for shift work is highest. For younger people it is easier to stand shift work.

With age the willingness to do shift work decreases. Reasons are health problems, disturbance of family bonds, social disadvantages and psychic stress. Often the time is too short to adapt to the shift work. To adapt to rotational shift work is especially difficult. Much more studies are needed for finding out optimal strategies for shift work (Rutenfranz (1978), Winget et al. (1978)). Furthermore the individual situation has to be taken into account (Fröberg (1977)).

7.3 Penalties of shift work

Negative consequences of shift work are:

1. The efficiency drops. This has adverse effects on work as well as on sleep. Consequently sleep disturbances occur frequently.

2. Shift worker have to adapt continuously to new situations. This is a stress for the circulatory system and the digestive system. Heart attacks and digestive tract problems occur more frequently. Meal can not be taken at the normal times. During night work snacks are often eaten.

3. The circadian rhythm is affected adversely: The normal course of the daily routines is work, leisure, sleep. In shift work, however, it is often work, sleep, and leisure. This is likely to be the cause of the difference in the course of body temperature of shift workers as compared to day workers. Furthermore the pattern of shift work is often unfavorable: If a new shift is earlier as the preceding one, it is badly tolerated by the circadian system.

To illustrate some of these points with examples:

- Astronauts have been trained to a 12-h-day with 6 h work, 2 h recovery and 4 h sleep. Since this rhythm is completely unnatural, it was not astonishing, that on the fourth to fifth day extreme tiredness and vegetative disturbances occurred (Dushkov and Komolinskii (1968)).

- Watches on American nuclear submarines were designed on the basis of a 18 h day (Schaefer et al. (1979)). Crew members did not tolerate this unnormal day at all and there was a high dropout rate. Officers lived in a normal 24 h day and had therefore no problems.

- The police in Stockholm (Sweden) worked according to a 20 h day, which was badly tolerated by the policeman (see in Eriksen and Kecklund (2007))

All these work cycles were a heavy stress for the involved persons. The reason was, that they were outside of the range of entrainment of the human circadian system[2]. Consequently the people involved were more frequently sick or they did even quit work.

The effectiveness is often reduced by shift work: The frequency of accidents increases, the error rate rises (figure 7.2).

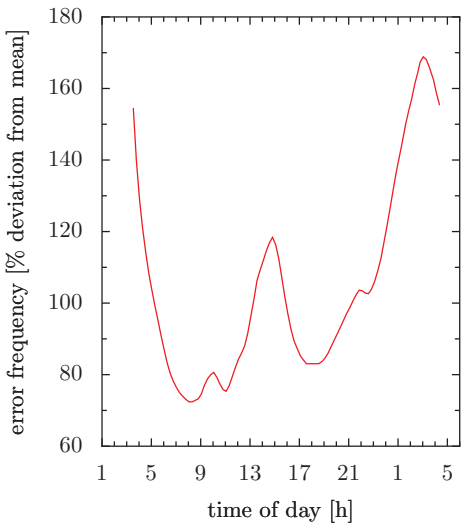

Figure 7.2: *On the y-axis the deviation of error frequency from the mean (in %) is plotted for 62000 shift workers in the industry. After Bjerner and Swensson (1953)*

Many serious accidents were caused by people which sinned against their biological clock: They were over tired (nuclear power

[2] range of entrainment lies between 22.5 to 26.8 h, although depending on light intensity also

plant accidents in Tschernobyl 1986 and in Three Mile Island 1979, the Challenger-space shuttle disaster in 1986, the accident of the oil tanker Exxon Valdez 1987) or they had fallen asleep (capsizing of the ferry Herald of Free Enterprise at the Belgian coast in 1987, running ashore of the Japanese oil tanker Matsukaze at Seattle 1988). Numerous car- and airplane accidents had similar causes (Zulley and Knab (2000)). (Zulley and Knab (2000)).

Rotating shift seems to be especially stressing. It would be better to have a permanent shift instead. This would allow a permanent and fixed synchronization of the daily rhythm. Permanent shifts are, however, so far frowned upon. A number of reasons (for instance social discrimination) are responsible for it, among them social discrimination. These disadvantages of shift work could, however, be avoided. Shift workers should get more time off. They should also get enough sleep, which is often not the case. It has for instance been reported that engine drivers sleep only 6.5 instead of 8 h.

Besides the consequences of a disturbed circadian rhythm there are secondary adverse consequences. They are caused by smoking, coffee and alcohol. Cancer rate is increased, which often does not show up before five years have elapsed. The percentage of sick shift workers is often underestimated because the ones who quit for health reasons are not counted anymore (self selection of shift work). Furthermore shift workers visit the doctor less frequently.

7.4 What can be done to avoid or reduce the unfavourable consequences of shift work ?

To start with, not all humans are to the same extent able to stand shift work. Younger people take it better as older ones do. Morning types have more difficulties with it as compared to evening types (figure 7.3).[3] Furthermore the circumstances of shift work can be improved. The weekend, for instance, should be structured in the same way as the shift work during working days. That is, if one works evening shifts, one should continue to stay up late during the weekend and go to bed late. Social Zeitgeber should be taken into account. Nor should other Zeitgeber be neglected. Sleep itself is important as a Zeitgeber. A so called 'anchor sleep' of a certain length (for instance from 00-04 o´clock, if normal sleep is from 00-08) has shown to have its merits (page 234 in Minors and Waterhouse (1981)). The remaining sleep can than be taken at different times and work hours taken in between the two sleep periods (figure 7.4). Other ways of optimizing shift work have been discussed by Åkerstedt and Fröberg (1977) and Monk (2000), to name a few. Machines and equipment have been and are constantly optimized, but unfortunately man who serves the machine has not

[3] The amplitude of the body temperature of evening types is as a rule larger. They tolerate therefore shift work better, because they adapt less or not to the changed conditions (Reinberg et al. (1978), Kerkhoff (1985)). A morning type, however, has normally a circadian rhythm with a low amplitude. In this situation the body tries to adapt to the new conditions (Östberg (1973)).

been given enough attention[4].

People belonging to risk groups should not be allowed to do shift work. To this group belong persons suffering under diabetes, respiration- and circulation problems, kidney problems, epileptics, schizophrenics, depressives.

In a review article (Monk (2000)) has put together different ways in which shift workers can be helped from their employers or help them self in avoiding these problems or at least reduce them. See also Costa (1997). Certain drugs which enhance alertness can countermeasure fatigue in shiftwork (Åkerstedt and Fröberg (1977)).

Ehrenstein (personal communication) proposed to organize shift work and night work anew. Shift work should be offered in a way that it would be done voluntarily. Instead of rotating shifts a permanent shift work should be introduced and used. The shift worker should be advised in respect to chronohygienic knowledge and the danger of this work should be pointed out to him. There should be uniform shift changes which are coupled to the onset of the school year. This would ease inter-familiar arrangements. If too few or too many workers enroll for a shift, the allowances must be corrected correspondingly. The weekly salary should not change, but there should be more or less working hours. There should be facilities available (for instance with special lighting conditions) in which the circadian rhythm of workers could be adapted to a new shift. The social environment must be made attractive in such a way, that the shift worker sticks to his daily scheme even at the weekend. In late and in night shift bright light exposure during the day should be avoided.

[4] ‘No responsible manager would consider operating a piece of machinery outside its design specifications, for that would lead to excessive wear, frequent breakdowns, and early replacement. Yet managers and workers alike have accepted as inevitable the physiological costs of shift work schedules that exceed the design characteristics of the human circadian system.´ (Moore-Ede (1986))

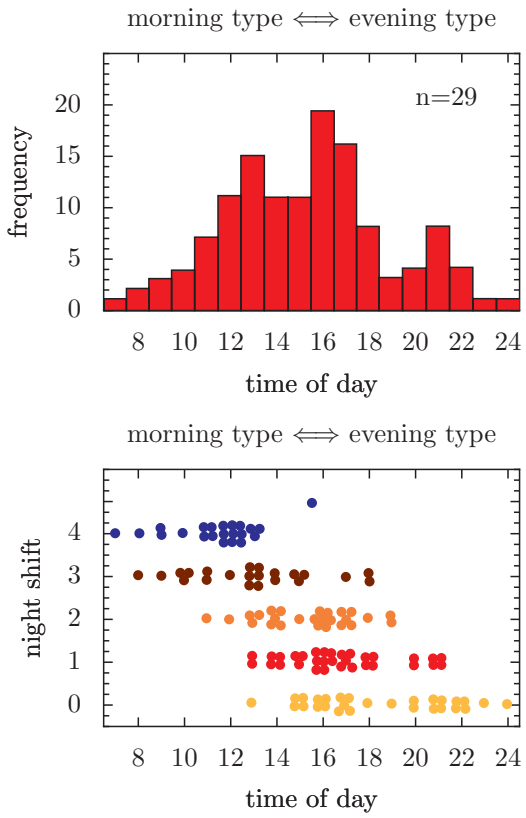

Figure 7.3: *Morning types stand shift work less well as evening types: In 129 nurses of a hospital the chronobiological phase type was checked (top curve; x-axis: score of phase type, left morning type, right evening type). Than these persons were asked, how they tolerated night shift (5 questions). The results (lower part of the figure) show, that morning types tolerate night shift less well as do evening types (4: avoiding night shift, 0: preferring night shift; x-axis: score of phase type, morning type left, evening type right). The correlation coefficient is -0.72. After Hildebrandt et al. (1998)*

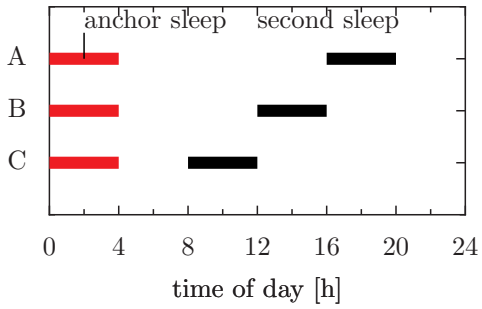

Figure 7.4: *An anchor sleep for a person who usually sleeps from 00 to 08 am would be from 00-04 o´clock. Work hours would follow or precede the anchor sleep, and an additional sleep period could be taken at various times as indicated by the second black bar. In this way disturbances of the circadian rhythm of body temperature are reduced considerably. After Minors and Waterhouse (1981)*

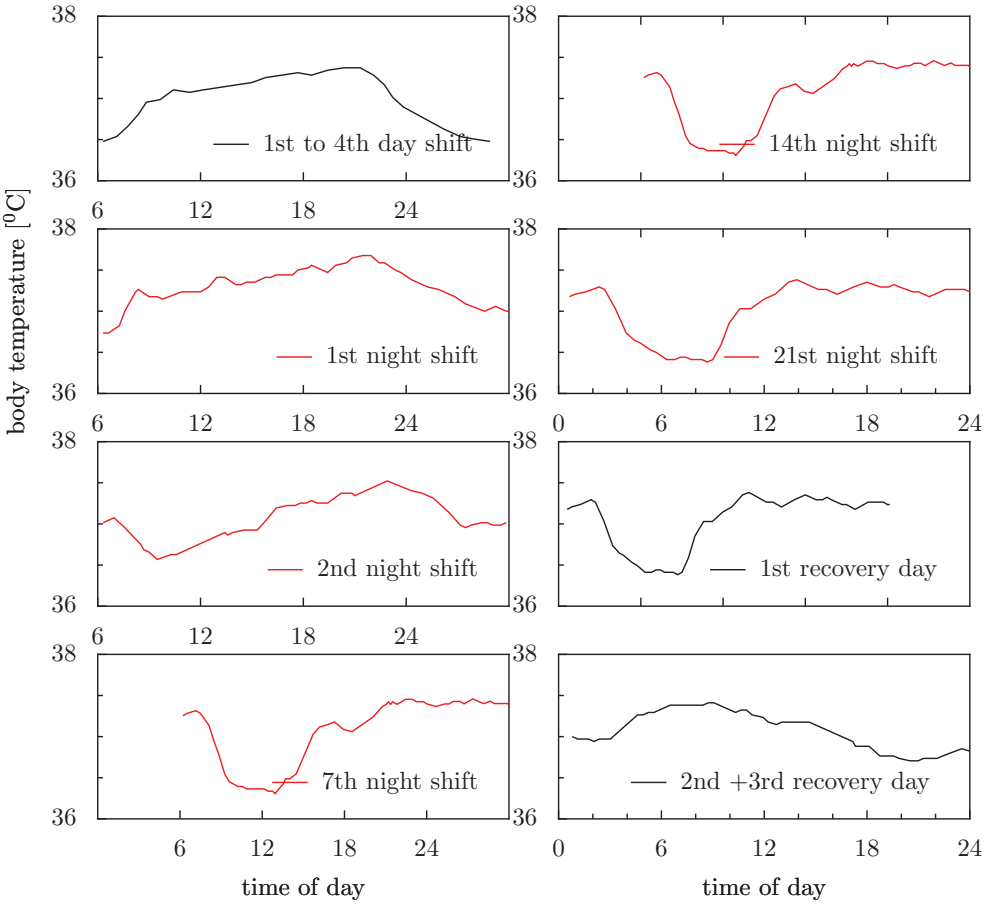

Figure 7.1: *Course of body temperature measured during 1-1-1 shift schedule: After a day of no work (black curve top left, blue horizontal line represents sleep time) one day of early shift work from 6:00 to 14:00 (green curve, center left), one day of late shift work from 14:30 to 22:00 (blue curve, bottom left) and one day of night shift from 22:00 to 6:00 (red curve, top right). Afterward two days off duty (black curves, right center and bottom). Body temperature values are means from four subjects. After Rutenfranz et al. (1977)*

8 Jetlag as a consequence of travelling through time zones

Everybody who has traveled through several time zones by flying east or west knows jet lag. One has to adapt to the phase shifted day-night conditions (figure 8.1 and table 8.1). In flying north-south the jet lag is lacking. Here only the stress due to flying is encountered.

Jet lag affects the passengers *and* the air crew. For the the crew the jet lag is not only annoying. Their efficiency is reduced and therefore the safety of the passengers endangered. About 65% of all air traffic accidents are due to mistakes of the pilots or the crew (Moore-Ede et al. (1982), Mitler et al. (1988)). [1]

Jet lag is due to stress and to effects on the circadian system as a result of traveling through time zones. The causes and symptoms are similar to the one in shift work.

The consequences of a reduced efficiency after a long distance flight crossing time zones is documented by the negotiations of Dulles in 1950 in Egypt. The American foreign minister had crossed 6 time zones to the east and was badly adjusted with his endogenous clock to the Egypt time. As known, the Assuan dam project was taken over by the former Sowjet Union. Diplomats, business man and sportsmen are also strongly affected by such flights crossing time zones.

For the traveler who stays for some time at the destination country the adaptation is easier as compared to a shift worker: The social time cues in the destination country help to adapt quickly (first described by Sharp (1960)). If a passenger stays for a longer time, as is often the case in travellers, he or she should try to adapt to the new time zone already *before* the actual flight by shifting each day the phase of the circadian rhythm for about 1 to 2 h. Flying from Europa to the USA, one should each day for about one week *before* the flight go to bed and rise one hour later. The time for adaptation in the destination country varies and depends on how one behaves. The light-dark-cycle (Daan and Lewy (1984)), the time and kind of food[2], drinks, medication[3], activities such as jogging (Mrosowsky and Salmon (1987)) play a role.

In contrast to the passenger who tries to adjust to the new time zone, for the crew which flies back soon, and for the passenger who has only a short stop, the situation is

[1] Mistakes in manual control are, by the way, rare. In most cases it is the lack of knowledge, communication errors, wrong decisions, or that available alternatives were not used. The current trend to auto-control lowers the motivation of the pilots, a further weak point in modern aviation.

[2] Phase shifts by combining multiple time cues. Food with high protein content promotes catecholamine synthesis (wake-time), high carbohydrate content promotes serotonin synthesis (sleep time). Methylxanthine containing drinks such as coffee, tea, cacao are also chronobiologically active substances (Ehret et al. (1975)).

[3] Jetlag-pills: Melatonin (Arendt (1997)), benzodiazepine (a sleeping drug, which inhibits GABA in the SCN, triazolam (Turek (1986)).

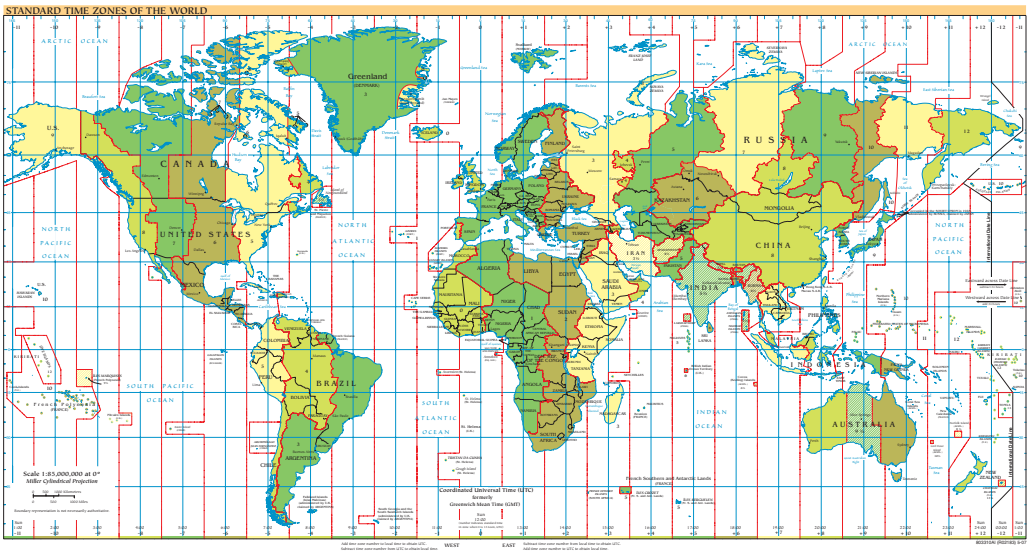

Figure 8.1: *Time zones of the earth. The figure shows the twenty four time zones of the earth (Greenwich, London=0) and the countries belonging to these zones. If it is, for instance, 1 o'clock at night in Germany (+1), it is 11 o'clock in New Zealand (+1 to +12 is 11 h difference). If it is 8 o'clock in the morning in Germany (+1), it is in New York (-5) 2 o'clock in the night (+1 to -5 is -6 h difference). For calculations see table 8.1). From* The world fact book CIA *under https://www.cia.gov/library/publications/the-world-factbook/reference_maps/time_zones.html*

different. This asks for a different strategy. Both groups should not adapt after a time zone flight. There are recommendations of the ICAO (International Civil Aviation Organization) for resting times of the air crew personal. However, individual adaptations are necessary. Furthermore personal factors are important such as lifestyle, motivation[4], emotional behaviour, professional experience, routine, geographical and ecological factors (climate, altitude), operational factors such as begin and duration of duty. The crew should avoid sleeping pills and alcohol. It is known that 40% of the stewardesses take sleeping pills. They affect sleep negatively. In connection with other medications the effects can raise to higher power. Autogenous training helps generally and also for short-term regeneration. A good self-observation is necessary. Even short sleep periods (6 h) are sufficient for regeneration. In short-distance flights the sleep should occur in isolation, to avoid effects of time cues at the destination place. In this way one keeps the time of the body[5].

Unfortunately there is still a lack of detailed information. It would be important to record body rhythms during the flight and to take notes regarding the sleep and tiredness. From these informations conclu-

[4] Too much attention is paid to the pilots. Instead the whole crew should be taken into account. Group dynamics, style of leadership, personality structure of the crew, kind of communication are important.

[5] The Aeroflot provided their pilots sleep in complete isolation and tried to avoid night flights, if possible

sions could be drawn how jet lag can be avoided or reduced. So far there are only a few physiological and biochemical data. These studies could also be performed on the ground (for instance Wever (1979), Mills (2005)). Simulations using models can be helpful (Gander et al. (1985), Klein et al. (1970), Johnsson and Fröberg (1974), Gundel and Spencer (1992)). For instance, there is a difference in adapting to new time zones depending on whether one flies east or west (figure 8.2 and figure 8.3). In a publication it was reported that among illnesses of travellers depressions are more frequent on westbound flights. Basis of these findings are medical treatments at the airport of Heathrow near London (Jauhar and Weller (1982)).

21	22	23	24	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
20	21	22	23	24	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
19	20	21	22	23	24	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
18	19	20	21	22	23	24	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
17	18	19	20	21	22	23	24	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
16	17	18	19	20	21	22	23	24	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
15	16	17	18	19	20	21	22	23	24	1	2	3	4	5	6	7	8	9	10	11	12	13	14
14	15	16	17	18	19	20	21	22	23	24	1	2	3	4	5	6	7	8	9	10	11	12	13
13	14	15	16	17	18	19	20	21	22	23	24	1	2	3	4	5	6	7	8	9	10	11	12
12	13	14	15	16	17	18	19	20	21	22	23	24	1	2	3	4	5	6	7	8	9	10	11
11	12	13	14	15	16	17	18	19	20	21	22	23	24	1	2	3	4	5	6	7	8	9	10
10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	1	2	3	4	5	6	7	8	9
9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	1	2	3	4	5	6	7	8
8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	1	2	3	4	5	6	7
7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	1	2	3	4	5	6
6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	1	2	3	4	5
5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	1	2	3	4
4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	1	2	3
3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	1	2
2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	1
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
24	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
23	24	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
22	23	24	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21

Table 8.1: *Time zones-table. The top row refers to the times given in figure 8.1. 0 (=24 o´clock) would be Greenwich time, 9 Tokyo, 19 Eastern America. If the time at a any place on earth is known, the corresponding time for other time zones can be found by checking the left or right columns (example: If it is 8 o´clock a.m. in Frankfurt, what is the time in New York? Frankfurt has central European time, therefore the column with 1 at the top has to be used. Go to 8 in this column, than in this row to the right until the column which contains the head number 19 (Eastern America). It shows that in New York it is now 2 o´clock a.m.*

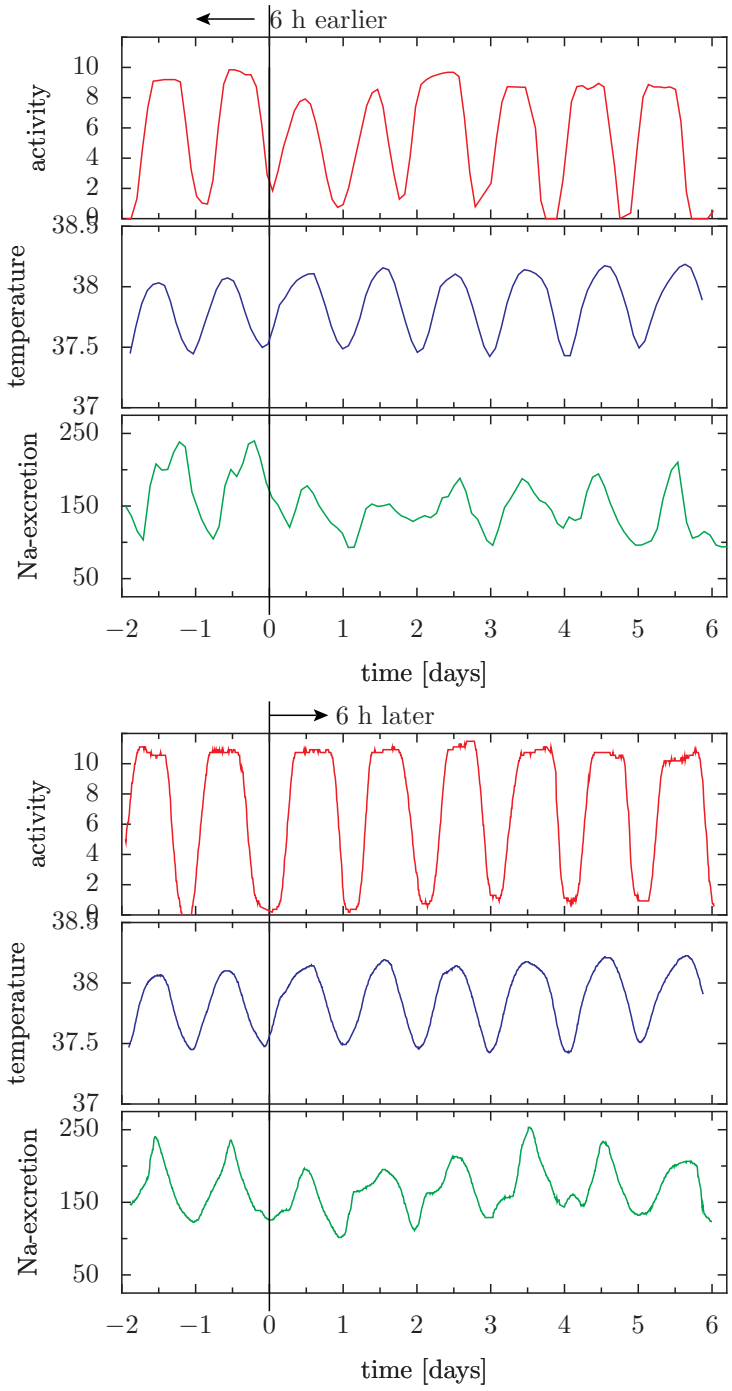

Figure 8.2: *Adaptations of body functions after east flights (top curves for activity (red), body temperature (°C, blue), and sodium excretion in the urine (mg/h, green)). Adaptations of body functions after west flights (bottom curves). Flight indicated by vertical red line. After Wever (1979)*

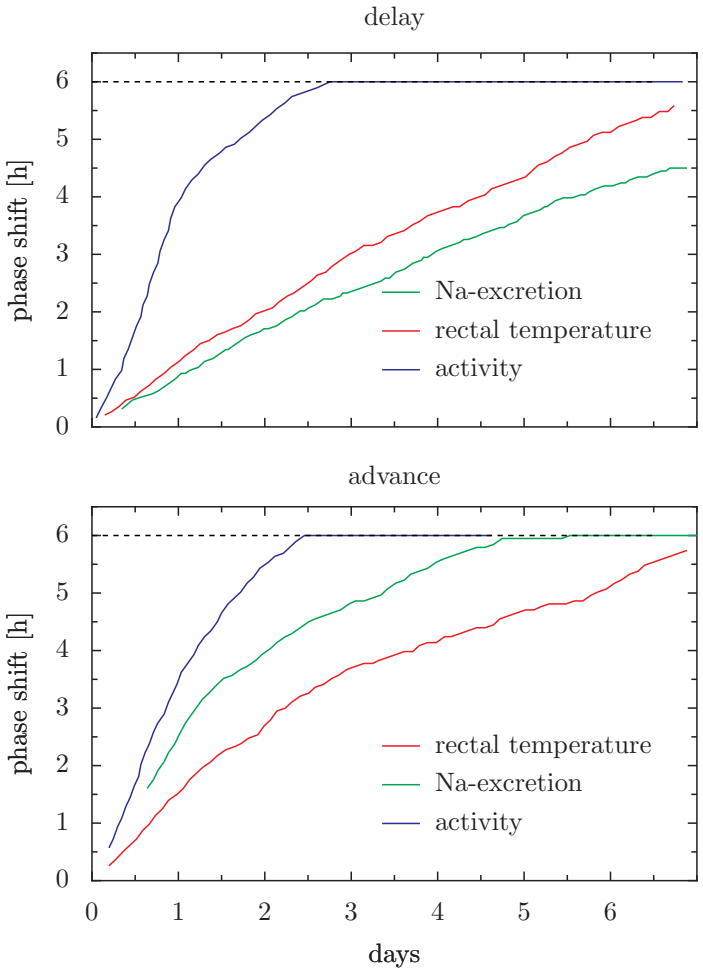

Figure 8.3: *Adaptations of body functions after flights: How long it takes until different body functions (activity (red), rectal temperature (blue), and sodium excretion (green)) adapt to the new time zones after east- (top curves) and west journeys (bottom curves).* After Wever (1979)

9 Significance of rhythms for healthy and sick men

Rhythms are utilizedby organisms to resolve certain tasks. For instance, daylength can be measured with a day clock and used to determine the season. This ability for photoperiodic timing plays an important role in very many plants and animals of the temperate and higher latitudes of the earth. In this way they are able to prepare in time for unfavourable environmental conditions and to survive for instance cold winters or dry and hot summers.

In the preceding sections we have seen some medical aspects in connection with shift work and jet lag, in which circadian rhythms are disturbed and health is affected. Sleep disturbances are among them. More about medical aspects are presented in this section (see Costa (1997)).

Since the sensitivity of the body toward many medications changes in a daily pattern, it is not unimportant at what time medication is taken. This is especially important in the case of medications which exert also a toxic effect as for instance in cancer therapy. Times of the day have to be found at which the substance is less toxic, but most effective against the cancer. Anesthetics, analeptica, corticosteroids, anabolic steroids, histamines and alcohol are further examples for substances, the effect of which changes in a diurnal way.

Chronopharmacology has become in the meantime a research area by its own and their results have to be taken into account by medical doctors while describing medication and treatments (Lemmer (1996); Hildebrandt et al. (1998)).

Pain is received differently at various times of the day (Jores and Frees (1937)). The heaviest pains are felt around 18 o'clock, whereas during the night and in the morning they are weaker. Since sensitivity against pain is centrally controlled, painful operations as for instance in the treatment of teeth should be made in the morning. Unfortunately the efficiency of the dentist is at that time not optimal (it reaches its optimum in the afternoon).

9.1 Chronopharmacology

In 1920 Otto Loewi discovered the chemical transmission of nerve impulses in a dream. On the next morning he had forgotten the details. In the next night he had the same dream. In order to avoid that he would forget again the details he performed the experiment straight away during the night at 3:00 in his laboratory: He stimulated the vagus nerve of a donor heart of a frog and demonstrated that by this treatment the heart rate of a recipient heart was slowed. If he would have done this experiment at an other time, the difference would have been much smaller or even insignificant, since this event is modulated by a daily rhythm. Together with Henry Dale he obtained for this discovery the Nobel price in 1936.

The body reacts to substances administered from outside such as aspirin, appetite suppressant, sleeping pills (barbiturate), amphetamine, endotoxine or poisons

quite differently, depending on the time of day. The pain appeasing effect of novalgin, for instance, changes in a daily rhythm (figure 9.1). The effect of X-rays does also vary at different times of the day. Here some further examples:

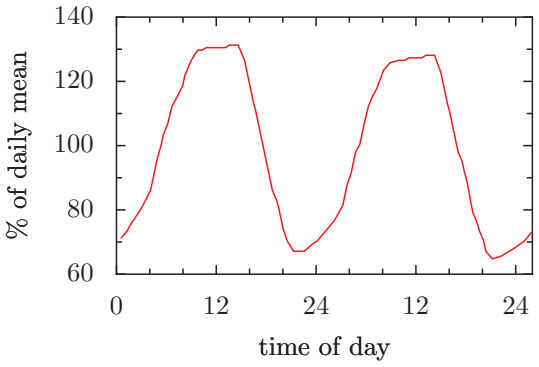

Figure 9.1: *The pain appeasing effect of novalgin (percent of the daily mean) is higher in the morning and early afternoon as compared to the evening and night. After Hildebrandt et al. (1998)*

- The pain appeasing effect of Novalgin is higher during the day as compared to the evening the night (figure 9.1).
- The effect of antihistaminic drugs stays for 15-17 h if the substance is given around 7:00, but only 6-8 h if given around 19:00 (Reinberg and Sidi (1966)).
- Digitalis has at night twice the effect as during the day.
- Glucocorticoids are more effective during the day as compared to the night and show less side effects.
- The optimal time for medication against cardiovascular, endocrine and other disturbances depends likewise on the time of application. Medication against to low blood pressure should be taken in the morning, when the blood pressure is at its lowest point. However, medication against to high blood pressure should be taken in the evening, when the blood pressure is highest.
- The toxicity of a substance can vary considerably. Neostigmin for instance has during the night a toxicity which is 50% higher as compared to its day effect. A chemotherapeutic against cancer, cytosine-arabinosid, has less toxic side effects if given at different times of the day in varying amounts as compared to the same dosage every three hours as was done before (Haus and Halberg (1972)).
- Undesired side effects of the adrenal hormone and synthetic corticosteroids can be reduced by the proper timing of administration: In this case it would be the time of waking up. At that time the adrenaline-secretion is maximal. In testing pharmaca the time of day has also to be taken into account.
- A high variability in studying the effects of pharmaca is partly caused by differences due to the daily rhythm.

The time of application of medications can and should thus be optimized.

On the other hand medications can also influence the rhythm. Quiadon, a sedative, which however increases activity and efficiency, is an example (Simpson et al. (1973)). Melatonin affects also the circadian rhythm (Lewy et al. (1992)). These substances help to adapt more quickly to phase shifts as a result of traveling through time zones. It is also conceivable that with a special chronotherapy only certain

rhythms are manipulated, whereas others stay unaffected. If internal desynchronization would cause certain diseases, the normal phase relationship could be re-installed by such pharmaca.

For more details see Reinberg (1974)Reinberg and Smolensky (1983).

9.2 Sleep disturbances and circadian rhythm

Sleep disturbances are frequently encountered[1]They are not only quite annoying, but evendangerous. Narcolepsy is an example, sleep walking another. Sudden infant death syndrome (SIDS) occurs during sleep. For more details on sleep disturbances and therapies see Eastman et al. (1995); Richardson and Malin (1996); Czeisler and Dijk (1995) and Kelly (1991a).

Sleep disturbances are classified into

1. disturbances of initiating and maintaining sleep,
2. insomnia,
3. hypersomnia (e.g. narcolepsy, sleep-apnoe, idiopathic hypersomnia),
4. disorders of the sleep-wake schedule and behavioral dysfunctions associated with sleep (e.g., especially in children, night mares, sleep walking, enuresis).

[1]About 15% of the population in industrialized countries complain about chronic, and 20% about occasional sleep disturbances. In the Unites States about 29 to 39% of the inhabitants older than 18 years suffer under it (that is 45 to 60 million people). 8 to 12 million of them are under medical treatment, 4 to 6 million use sleeping pills. In 1977 about 25.6 million sleeping pills were prescribed, and another 30 million which were bought without prescription.

Here some remarks to sleep disturbances connected with the circadian system:

Temporary insomnia is often the result of changed phase relationship of the sleep in respect to the day-night-rhythm. This relationship can be disturbed in shift workers (see section **??**) and by jet lag (see section **??**). In the case of delayed sleep phase syndrome, falling asleep is disturbed. It occurs often in persons belonging to the evening type. They do not have problems if they fall asleep for instance between 4:00 in the morning and 12:00 o´clock. That is, their sleep per se is not disturbed. It is only wrongly adjusted to the day-night rhythm. In such cases a therapy is adequate in which the rhythm is normalized again. Sleep disturbances of many shift workers could be cured by using better shift schedules, as discussed in section **??**.

Even the ‘normal´ sleep pattern might not be optimal. There are indications, that a siesta in addition to the night sleep is more natural (figure 9.2, Wehr et al. (1993)) and more relaxing (Strogatz et al. (1987)). It is wide spread in the mediterranean countries and more pronounced in the elderly subjects (Carskadon and Dement (1987)).

In some cases the sleep time of a person is not synchronized to the 24 h day. Instead those persons show free run with a period length according to the speed of the circadian clock. Those people have sleeping difficulties during periods where their active phase coincides with the normal night time (Kokkoris et al. (1978)). The sleep of blind persons is often disturbed for the same reason (see section **??**).

Sleep disturbances were found in humans with certain mental diseases (Roth and Roehrs (2000)) such as schizophrenia[2]

[2]schizophrenics go to bed earlier and rise up ear-

(Roschke and Aldenhoff (1993), Dealberto (1992), Keshavan et al. (1990)), epilepsy (Bazil (2003)) and endogenous depressions[3] (Southmaid et al. (1991), Roschke et al. (1994), Goldenberg (1993); see also section 9.4). In narcoleptics (Kahn et al. (2001)) the circadian system is changed, but principally intact[4]. Schizophrenics go early to bed and rise early. Manic depressives go to bed late and rise late.

.

9.3 Seasonal affective disorders and light therapy

Besides endogenous depression there exist also depressions which are known as 'Seasonal Affective Disorders' (SAD). Here we are dealing with a disease which is less severe and less noticeable as compared to endogenous depression. Its distribution is heavily underestimated, because the affected people will seldom see the doctor. SAD was described in 1982 by Rosenthal et al. (1984). The disease begins in the late fall and winter (October to December in the northern hemisphere) and ends in the spring (March in the northern hemisphere). In most cases it is a mild depression. There are, however, also severe cases. This depression depends on the latitude. It is found often in persons who live in higher latitudes in the northern and southern hemisphere (Teng et al. (1995)[5] The following symptom are characteristic: The activity of the patients is reduced, they go to bed earlier and rise up later; sleep is thus prolonged. The sleep structure has changed: Latency is longer, REM density increased, the delta sleep reduced. These patients have difficulties to concentrate during their daily work. They are unsociable. The neuroendocrine system is, however, normal which contrasts with the typical depressive person.

During the winter they show 'hunger for light' (Wehr and Rosenthal (1989), Lam and Levitt (1999)). SAD patients are more sensitive to variations in the length of the natural day (Guillemette et al. (1998)). They are super-sensitive to light during the winter (Terman and Terman (1999)). It was supposed that changes in photoperiod induce SAD and that the duration of melatonin secretion mediates the effect of photoperiod on behavior (see Wehr (2001) and section 5.8). The effects seem to be more pronounced at higher latitudes (review Lam and Levitan (2000)). In 60% of the patients a photo-therapy with bright light during the winter is successfull in treating SAD (Terman et al. (1998)). The effect is mediated by the eyes (Wehr et al. (1987)). It is assumed that light therapy in SAD-patients acts via melatonin. The melatonin pattern of patients differs between summer and winter, but shows

lier

[3] manic-depressives go to bed later and rise up later

[4] Narcoleptics suffer under sudden short sleep attacks during the wake time. These attacks are connected with a low muscle tonus ('cataplexy´) and last usually for 10-20min. An empty glance is typical. During an attack the EEG is REM-sleep-like. Apparently in narcoleptics the ultradian rhythm of the REM-sleep is not normal, but fragmented and extends into the wake period (Reid et al. (1998)). After the attack the affected person feels refreshed. Routine work is continued, but done with many errors. Because of the atonia this condition might lead easily to car accidents. In about 0.04 to 0.09 % of the cases of narcolepsy the affected persons fall into coma. Having a short nap during the day narcoleptic attacks can usually be avoided (Naitoh et al. (1969)).

[5] but see also Magnusson and Boiwin (2002) and the references therein

no difference in healthy individuals (Wehr et al. (2001), see however discussion in Magnusson and Boiwin (2002)).

Different photo-therapies were used. According to one method the patients were illuminated with light of 25000 lux for 3 h in the morning before sunrise and in the evening before the usual time to go to sleep. The depression improved after 2-4 days. The same effect was gained by 1 h light with 1000-2000 lux two hours before the normal wake-up time. Light in the evening is also effective. There are, however, also reports of experiments which speak in favor of a placebo effect of the light. There were no significant differences in the effect of weak (30, 400 lux) and stronger white light (6000 lux) and between weak red light and stronger white light, which was administered in the morning to SAD patients (Rosenthal et al. (1993), Joffe et al. (1993), Teicher et al. (1995)). It does not seem to matter whether the light is applied in the morning, at noon or in the evening (Lewy et al. (1998), Meesters et al. (1995), Thalen et al. (1995)); see however Leibenluft et al. (1996). The treatment should last at least one week, but preferentially three weeks (Eastman et al. (1998)). Dawn simulation improves the efficiency of the light treatment (Meesters (1998)). The most favorable effect of the light therapy is found at the lower range of high temperatures.

Another form of SAD is known where the patients become depressed in the summer (Wehr and Rosenthal (1989)). It has been much less studied than winter SAD. Summer depression is more frequently found in *lower* latitudes. It was suggested that high temperatures and not photoperiod may be responsible (Lam and Levitt (1999)). Since the seasonal patterns of human reproduction and of SAD are alike, they might have a common biological reason.

It is interesting that the main season of conception for children of SAD patients is in the late summer (studies on 219 patients in the United States), whereas normally the maximum is found in December. SAD was therefore regarded as a remnant of a seasonally dependent reproduction (Pohl and Giedke (1987)). In human societies it might have been advantageous to withdraw at times of food shortage, to have no children during this time and to reduce the energy consumption. All this are symptoms of SAD-patients. Eskimo women do even today not menstruate during the winter.

What is special about SAD? Is it a disturbance of the synchronization of the circadian systems?[6] Or is the circadian system changed, for instance desynchronized, changed in amplitude or phase advanced or delayed in respect to the norm (Bunney and Bunney (2000), Koorengevel et al. (2000), Thompson et al. (1997))? Light therapy (Lam et al. (1997), Partonen and Lonnqvist (1996)) or outdoor light (Wirz-Justice et al. (1996)) would in this case re-initiate or re-synchronize the rhythms.

Furthermore, in SAD patients the serotonergic system of the brain seems to be distorted (Schwartz et al. (1998), Neumeister et al. (1997)). Administration of serotonin uptake inhibitors is an effective therapy (Thorell et al. (1999)). However, both the light and the serotonin uptake inhibitor treatment does not work in severely ill patients (Schwartz et al. (1996)).

The melatonin concentration in the blood differs between winter and summer. It could be, that in SAD patients the illumination during the fall and winter is not sufficient to suppress melatonin.

[6] Does for instance the retina of SAD patients show special features? Or are social time cues too weak to synchronize the rhythm in these patients?

SAD seems to be heritable (see references in Magnusson and Boiwin (2002)).

Many questions concerning the relations between light, SAD, and the circadian clock remain unanswered (see Levitt et al. (1996), Lee et al. (1997), Meesters et al. (1999), Magnusson and Boiwin (2002)). Several types of SAD are known. Some of them react poorly to light treatment (Terman et al. (1996)). For special literature on SAD see Neumeister et al. (1998), Wirz-Justice and Graw (1999), Zulley and Wirz-Justice (1998) and two articles in Touitou (1998). For practical aspects of therapy see Lam and Levitan (2000), Lam et al. (1997), Rosenthal and Oren (1995), and Dalgleish et al. (1996). Recent reviews are Magnusson and Boiwin (2002) and Partonen and Magnusson (2001). The effect of light is reviewed by Lam (1998). See also the website of the Canadian Consensus guidelines for the treatment of SAD (Lam and Levitt (2002)).

9.4 Endogenous depression and lithium-salts

Much more severe as compared to SAD are endogenous depressions. The patients feel sad, hopeless, are pessimistic, feel guilty, are often self-preoccupied and avoid social contacts. Energy, activity and libido are reduced, concentration and memory impaired, sleep is disturbed.

There are a number of findings, according to which the circadian system shows specialties in endogenous depressions (Halaris (1987)). According to one hypothesis they are caused by disturbances of the coupling of the two oscillators of the circadian system: They are out of phase. As a result the other rhythms can not be synchronized by the 24-h day. The cause of the disturbed phase relationship is according to *Kripke (1984)* an oscillator which is too fast (period length only 21.8 h). This disturbs the sleep pattern, and the maximum of the body temperature lies earlier. The depression occurs if the maximum of the body temperature is after midnight. Mania occur, if the maximum is in the afternoon or in the evening. The sleep duration depends on the phase in which sleep begins. It will be short if sleep begins in the minimum of the body temperature. It will be long, if it begins in the maximum. In healthy people depression like symptoms and anomalous sleep patterns can be induced if they have to sleep from 10 o'clock onward.

Endogenous depressions can be treated if the sleep begins several hours earlier. The body temperature-rhythm and sleep-wake cycle are then synchronized again with each other. The airport hospital reports from Heathrow (Jauhar and Weller (1982)) speak also in favor of this hypothesis.

Endogenous depressions are treated successfully with Li^+-salts. They lengthen in a number of different organisms the circadian clock. It was assumed that they affect the circadian system also during the therapy of endogenous depression in man. We have studied therefore in an experiment in Spitsbergen (continuous light conditions during the summer), whether Li^+-salts slow the circadian rhythm of man (Halaris (1987)). This was indeed found (Johnsson et al. (1979, 1980)). It was speculated, that Li^+-salts affect the coupling between oscillators in the circadian system (Engelmann et al. (1983)). Later it was also shown in monkeys that Li^+-salts slow their circadian rhythm (Welsh and Moore-Ede (1990)).

Manic-depressive patients, especially women, are super-sensitive to light. Depressions are also found more frequently

among women. Perhaps women need more light for the synchronization of their rhythms (Kessler (2003)).

Besides these differences there are also a number of biochemical and physiological specialties. Patients suffering under endogenous depressions[7] have lower concentrations of the monoamine serotonin and noradrenalin in the brain in respect to healthy persons. The density of noradrenalin-receptors in the cortex is increased. The hypothalamus-hypophysis-adrenal axis is deregulated, because due to increased stress (genetic disposition, problems in the childhood) more CRF is excreted. As a consequence more cortisol ('fight-flight-hormone') is produced (Nemeroff (1998)) (figure 1.9).

9.5 Schizophrenia as nocturnalism

An ethological hypothesis was put forward, according to which the mental disease schizophrenia is a kind of nocturnalism (Feierman (1982)). It is claimed that schizophrenia is a condition in which the brain behaves during the wake state and in light as if it is sleeping. This hypothesis predicts an improvement, if light is kept under a threshold value.

Schizophrenia is the most common mental disease (Kraepelin (1896), Bleuler (1911)). 1% of the population shows it phenotypically. There is so far no way of treating it successfully. Schizophrenics are asocial and solitary. They have wrong (illogical) ideas ('delusions'), interpret sensory perceptions wrongly ('hallucinations), although they perceive correctly (short term memory is not affected). In their nonverbal behavior they show inappropriate affective behavior, the motoric pattern is funny, sometimes bizarre. Schizophrenics think unorderly, are not goal oriented, normal associations between ideas are disturbed ('tangential thinking').

Schizophrenia is determined by a genetic and a non–genetic component. So far there are no clear biochemical and/or morphological correlates, by which schizophrenics and normal people can be distinguished.

Feierman (1982) proposes, that schizophrenia is not brought about by an inherited metabolic malfunction. Instead it is a phyllogenetic adaptation: The brain uses normally new informations of the environment during wakefulness and stores it in the short term memory of the limbic system. During sleep these stored informations are symbolized and categorized. Afterward they are stored during the P-state ('programming mode') in the long term memory (using cerebrospinal proteins?). Schizophrenics perceive informations of the environment with a brain in the P-state, if wake during light. From a genetic standpoint they are, however, nocturnal: During darkness they would be in the active non-P-condition, which normal people experience during the wake state in the light (and in the dark) (see table 9.1).

This means perhaps from a phyllogenetic view, that for a social animal living in a group such as man it is more favorable if a part of the group members is night-active (protecting the group, hunting during the night). A number of indications are in favor of this interpretation: Many schizophrenics are born during the winter

[7] 5-12% der Männer and 10-20% der Frauen in den USA hatten mindestens einmal im Leben eine schwere depressive Episode, die Hälfte dieser humans mehr als einmal. 30800 Personen nehmen sich jedes year in den USA das Leben. Die Kosten beliefen sich 1992 auf 43 Milliarden Dollar.

	diurnal		nocturnal	
	light	dark	light	dark
sleep	P	P	P	wP
wake	NP	NP	*P*	NP

Table 9.1: *Condition of the brain of normal (genetically diurnal) and schizophrenic (genetically nocturnal) persons during sleep and wakefulness in the light and in the dark. After Feierman (1982)*

(photoperiodic influence?). Among blind people no schizophrenics are found. Likewise, under narcoleptics with a polyphasic sleep pattern schizophrenics are absent. Many schizophrenics are more active during sleep as compared to the wake time. The muscle tonus is not suppressed during REM sleep. In the light or in weak continuous red light the symptoms of schizophrenia should disappear. Perhaps schizophrenics possess a special visual system in respect to its anatomy?

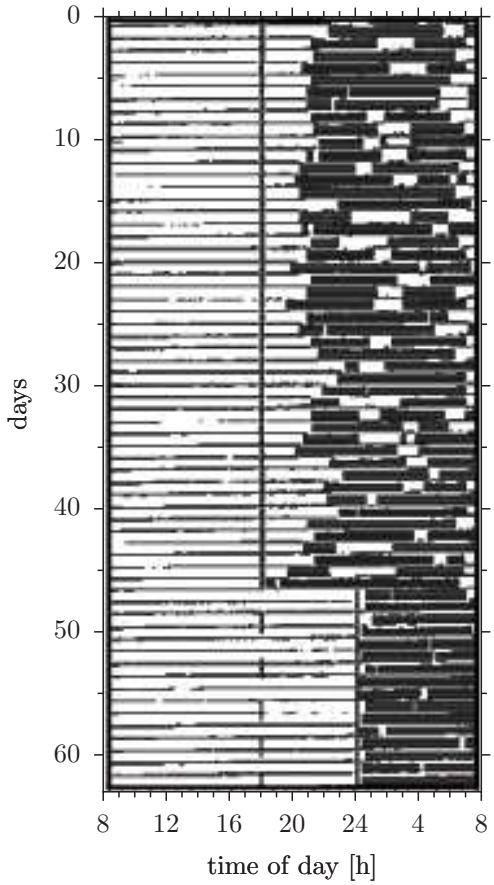

Figure 9.2: *Sleep of a young woman under long artificial 14 h nights, upper part, and under 8 h nights (bottom). The black bars show electrophysiologically monitored sleep. Note the bimodal sleep pattern in the long nights with 3-5 h sleep bouts separated by 1-2 h of wakefulness. This might have been the normal sleep pattern before the industrial revolution where many people slept from sunset to sunrise. After Wehr et al. (1993)*

10 Proposals for observations and experiments

Here I propose a number of observations and experiments, which should motivate you to deal with this interesting field in more detail. Already the Romans knew, that the best way to learn something is by doing it:

> Verba docent
> exempla trahunt[1]

In the following it will be shown, how the daily rhythm of a baby can be observed, how the chronobiological phase type of a person can be determined and how to find out whether we possess a head clock.

10.1 Daily rhythm of a baby

If no time cues of the environment are available any more (for instance, if we stay for some days in a cave (Siffre (1975)) or in well insulated bunker (Wever (1979), Moore-Ede et al. (1982)), we would notice, that we still go to bed and rise up in a daily rhythm. Likewise our body temperature, the amount of urine and the concentration of its constituents, our physical and mental efficiency would also cycle in such a rhythm (Aschoff (1973), Aschoff (1983)). However, the period length[2] would under these conditions be not any more exactly 24 h as found in a normal day/night-cycle. Instead the period would now deviate from 24 h and amount for instance to 24.3 h in a particular person, in another one perhaps 24.7 h. This 'freerun period' is specific for each person and under freerun-conditions normally longer than 24 h (see page 1). As soon as we are again under the influence of time cues, our daily rhythm is exactly 24 h. There are occassionaly exceptions: Persons, who exhibit a freerun of the daily rhythm in spite of time cues. This is observed in some blind people, but occassionaly also in sighted people. A further exception are newborn children.

In babies the sleep-wake-rhythm is not a daily one with sleep mainly during the night. Instead a baby sleeps in batches of several hours distributed over the day, and drinking has the same rhythm. With time a daily rhythm arises, which superimposes this 'ultradian rhythm´. The daily rhythm is, however, not yet synchronized to the 24-h day, as shown in figure 10.1. It takes several weeks until the baby is able to follow the 24-h day .

The activity of babies can be recorded with pressure-sensitive matrasses, which can be bought (but ar expensive). With some skill pressure sensors can be mounted beneath the matrass.

It is, however, easier, if the mother makes notes, at what time her baby sleeps or is awake and at what time it drinks. If she take cues from the baby and does not use her own ideas, the recorded data will show, whether and at what time the baby has developed a synchronized daily rhythm.

[1] words instruct, examples bring us foreward
[2] for instance the time between two following temperature maxima

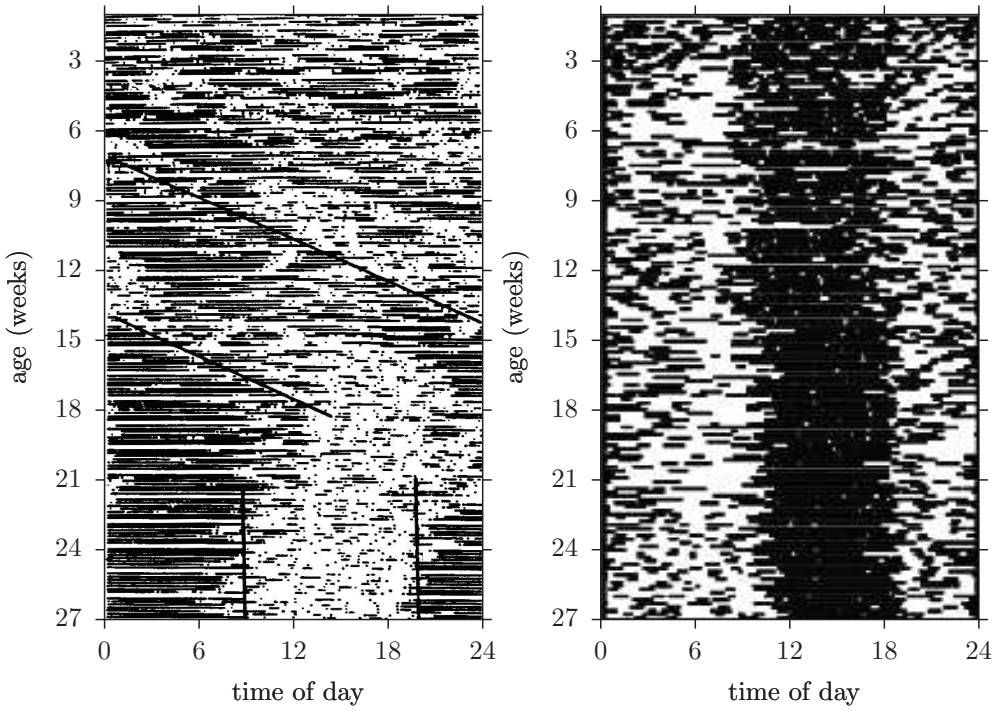

Figure 10.1: *Sleep-wake pattern of two babies in the first 26 weeks of their life. Left example after Kleitman (1963), changed. In the first 16 weeks the sleep periods (—) are chracterized by frequent awakenings. A 'freerun' of about 24.5 h is observable between week 9 and 18. From the 22nd week onward the baby is synchronized to the 24-h day. The times of activity are mainly during the days, the sleeping periods during the night, the parents can relay. Right example: Data of Marimuthu in Madurai, South Indiea. Here the baby is already synchronized to the day-night-ccyle in the first days after birth*

10.2 Lark or owl?

We will perform a test which shows you to which chronobiological phase type you belong. Fill out thequestionair (see page 68). The chronobiological phase type is the result of the sum of the scores (in paranthesis at the begin of a question) and is presented in table 10.1. Age, sex, profession, working hours and order of events during the day should be noted after results of several people are available (for instance of pupils of a class). If one would record simultaneously the daily rhythm of body temperature (with particular devices, which are to expensive for the layman), a special relation between the time point of the body temperature-minimum in the night and the chronobiological phasen type would turn up (figure 10.2). In evening types the minimum occurs later, in morning types earlier. These results are important in respect to problems of shift work, since it has been found, that extreme morning types are completely unsuited for late shifts (Åkerstedt and Fröberg (1977), Döhre (1977), Knauth and Rutenfranz (1975), see also chapter 7).

Other practical application can arise out of this finding. There are indications, that

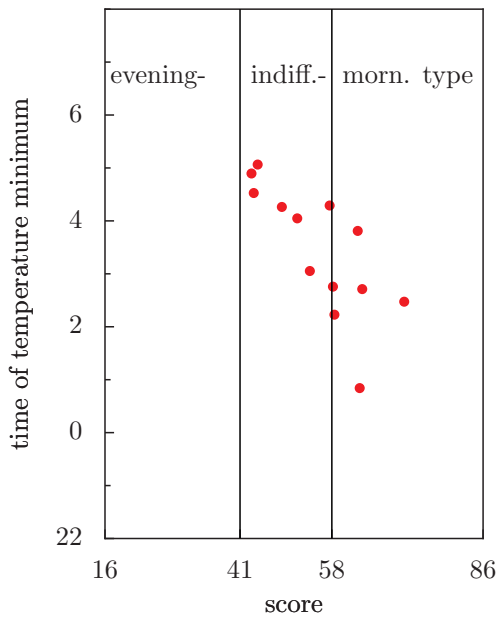

Figure 10.2: *Abhängigkeit des Zeitpunktes des nächtlichen body temperature-Minimums (Ordinate) vom chronobiologischen Phasentyp (evening-, Indifferenz-, Morgentyp). Die Zahl 16 repräsentiert einen extremen Abendtyp, die Zahl 86 einen extremen Morgentyp*

the chronobiological phase position of humans depends also on its age and undergoes changes during the school time. This is unfortunately not enough taken into account in our societies. It is likely, that many traffic accidents of pupils could be avoided, if the school times would respect the chronobiological situation in the children. Of course, the efficiency of the pupils does depend heavily on the phase of the daily system. This can be easily demonstrated by experimts. Here are a lot of interesting and important possibilities for studies. Somebody has claimed, more marriages would split, because the partners belong to different chronobiological phase types as for other reasons.

A detailed description of these experiments can be found in the book Engelmann (1999).

Questionair of the chronobiological phase type

This list consists of questions which are related to your activity and how much you feel awake in the morning and in the evening. In answering questions 1 to 4: Assume that you can work eight hours per day at times you are free to choose. Answer all questions. Cross only one answer. Be honest.

1. **How difficult is it for you if you have to go to bed each day at 1:00 o'clock**
   - (4) Very difficult. I would be terribly tired for a long time
   - (3) Quite difficult. I would be tired for some time
   - (2) Not difficult. I would feel slightly tired
   - (1) Not difficult, no problem
2. **How difficult is it for you if you have to rise up each day at 6:00 o'clock?**
   - (1) Very difficult. I would be terribly tired for a long time
   - (2) Quite difficult. I would be tired for some time
   - (3) Not difficult. I would feel slightly tired
   - (4) Not difficult, no problem
3. **You have decided to participate in a fitness-training. Your friend proposes to train twice per week. For him/her the best time would be from 7 to 8 in the morning. How would this be for you?**
   - (4) It would be optimal
   - (3) would be all right
   - (2)I would have difficulties, I would prefer a later time
   - (1) It would be to hard for me
4. **You have decided to participate in a fitness-training. Your friend proposes to train twice per week. For him/her the best time would be from 23 to 24 in the evening. How would this be for you?**
   - (1) It would be optimal
   - (2) would be all right
   - (3)I would have difficulties, I would prefer a later time
   - (4) It would be to hard for me
5. **Mark the time span in which you *normally* go to bed. The uppermost row is an example for somebody who normally goes to bed between 23:00 and 24:00.**

example ———												
20		21		22		23		24		01		02
(5)–>				(4)–>		(3)–>		(2)–>		(1)–>		

6. **Mark the time span in which you *normally* wake up.**

———											
05		06		07		08		09		10	11
(5)–>				(4)–>		(3)–>		(2)–>		(1)–>	

7. **Are you a morning- or evening active person?**

   - (5) extremely morning active
   - (4) moderately morning active
   - (3) neither
   - (2) moderately evening active
   - (1) extremely evening active

The values in parenthesis should be summed up (in the examples of question 6 one would use (4) and not (5)). The chronobiological phase type can be determined using the sum of the scores in the following:

- 7-10 extreme evening type
- 11-14 evening type
- 15-21 indifference type
- 22-25 morning type
- 26-31 extreme morning type

For evaluating the questionair see table 10.1[3]

Table 10.1: *Evaluation of the chronobiological phase type by using the results of the Dutch questionair*

Chronobiological phase type	score
extreme evening type	7-10
evening type	11-14
indifference type	15-21
morning type	22-25
extreme morning type	26-31

[3]This table should be available only after the questionair has been filled out

10.3 Our head clock

Bees possess a time sense: They are able to remember certain times at which nectar or pollen was available at particular plants. Man seems to have also a time sense. Anyway it is claimed, that some people are able to wake up at a certain time of the night with the help of a 'head clock' but without using an alarm clock (Clauser (1954)). They would for instance tell themself, I would like to wake up this night at 3 o'clock. Often they use additionally certain tites. They would, for instance, knock at the edge of the bed three times before going to bed. These people fall asleep completely normal, sleep deep and well and awake briefly before or after the planned time of waking up (figure 10.4). Clausen has ascribed this ability to a *head clock*, which might function in humans in a similar way as in bees and can be used as an alarm clock.

Perhaps you possess also a head clock? In this chapter it is shown how you can find out by using a slightly modified alarm clock. Use a battery driven alarm clock. Plan in the evening, at which time you want to wake up. The alarm clock is set to 12 o'clock. It stays at that time, because between the contact of the battery and the battery holder a piece of cardboard has beenm inserted (figure 10.3). Therefore no current flows. This cardboard is drawn out in the night when you wake up (assuming it is the planned time). Do not look at a running clock and continue to sleep.

On the next day you check the time of your alarm clock and count the hours back. This tells you, at what time the clock was activated, when the contact to the battery was made. If you had planned, for instance, to wake up at 4:30 and your alarm clock shows at 8:00 in the morning 3 o'clock, than you woke up three hours earlier, that is at 5:00 o'clock. You would have woken up half an hour too late.

In figure 10.4 some examples are shown of people, who were able to wake up quite accurately at the planned time (0 in the figure).

It is not yet known, whether the head clock in humans is identical with the circadian clock. This could perhaps be tested, if a person with a reliable head clock would test the wakeup time after east-west- or west-east-flights a day after the flight. The circadian clock needs a few days, until it is reset to the new time zone. One would expect a wrong wakeup time in respect to the local time, because the circadian clock is still at the former local time. If, however, a kind of hour glass (intervall-timing) is used, this head clock should work immediately after the flight across time zones.

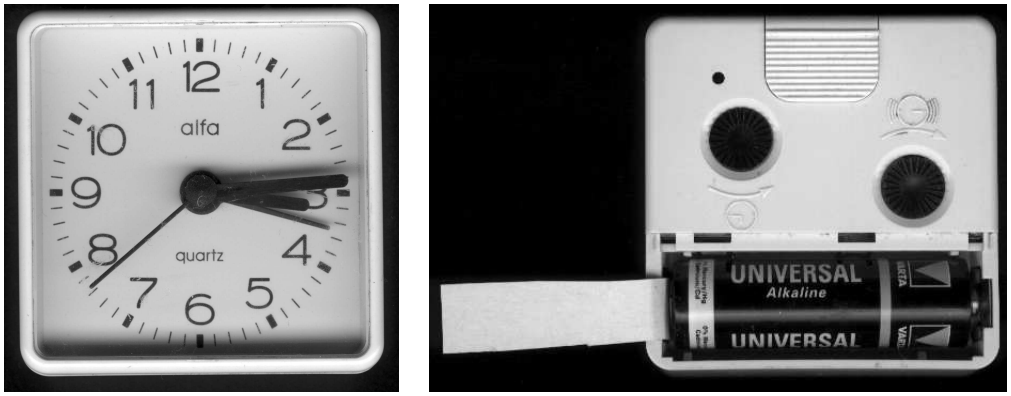

Figure 10.3: *The alarm clock is set to 12 o'clock and a piece of cardboard inserted between battery and battery holder. If the cardboard is removed in the night at the wakeup time (planned: 3:30 o'clock) , the alarm clock begins to run, because the contact to the battery exists again. On the next day you need to look only at the alarm clock (for instance at 8 o'clock in the morning) and count the hours back (here: 3 h 14 minutes), in order to know, at what time in the night the clock was activated, that is, at what time you woke up (8:00 minus 3:14 = 4:46 o'clock, that is 1 h and 18 minutes after the planned wakeup time. In this case this would not speak for a particularly accurate head clock. Anyway the train would have left if you would have relied on your head clock*

11 Further books

I have written further books or am in the process of writing. They are also concerned with topics, which have to do with rhythmic events in organisms - my specialty as a scientist (Engelmann (2007), Engelmann (2004c), Engelmann (2009a), Engelmann (2009b), Engelmann (2009c), Engelmann (2009c), Engelmann (2008), Engelmann (2004a), Engelmann (2004d), Engelmann (2004b)).

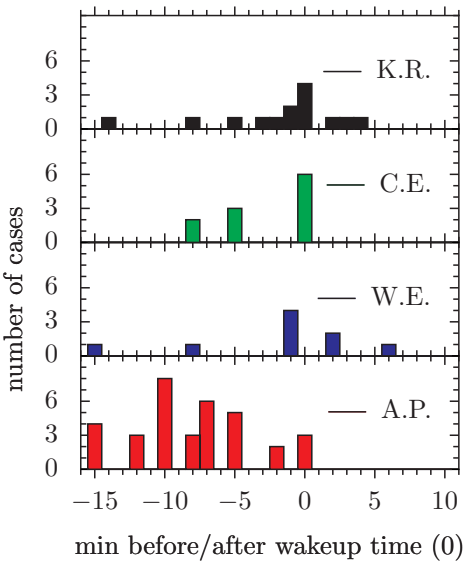

Figure 10.4: *Some people possess a head clock. It allows them to wake up during the night at a planned time without using an alarm clock. Here are some examples shown, in which the four persons A. P., W. E., C. E. and K. R. used their head clock quite efficiently. On the horizontal axis the time is plottted, at which the person woke up (0 is the planned time, for instance 4:00 o'clock in one of the persons, 2:30 o'clock in another). At the vertical axis is shown, how often and at what time the particular person woke up. C. E. for instance woke up in one night 15 minutes before the planned time. In another night it was 8 minutes earlier. In four further nights the person woke up 1 minute in advance, in two nights one minute past the planned time. In two further nights the wakeup time was 6 minutes too late. After Clauser (1954)*

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