A feeding-entrainable circadian oscillator system in the rabbit

Burghart JILGE

Laboratory Animals Research Unit, University of Ulm, Ulm, Germany

Summary - One of the most important properties of biological oscillators is their entrainment by exogenous forces acting cyclically in the environment. Among the environmental cycles, the phenomena recurring with a circadian periodicity are very prominent. The role of circadian zeitgebers is discussed giving a particular importance to the effects of feeding as a cause of masking and entrainment.
Ked words: Circadian rhythms, oscillator systems, zeitgebers.

Riassunto *(Rifasamento nutrizionale dei sistemi oscillatori circadiani nel coniglio).* - Una delle più importanti proprietà degli oscillatori biologici è la capacità di sincronizzazione. Questa è indotta da fattori ambientali a ricorrenza ciclica. Tra i sincronizzatori ambientali quelli con ciclo mediano sono prominenti. Tra questi ha un grande ruolo sincronizzante l'alimentazione. Gli effetti dell'alimentazione sui cicli biologici sono riportati in questo lavoro nei loro aspetti riguardanti il masking ed il riposamento.
Parole chiave: ritmi circadiani, sincronizzatori, sistemi oscillatori.

Circadian rhythms, zeitgebers and oscillator systems

Within the boundaries of homeostasis most physiological, endocrine and behavioral functions of animal and man exhibit significant 24 h rhythms. The amplitude of a particular rhythm can amount to several hundred percent (e.g. melatonin, STH, gastrine, food intake). Thus, whether one is measuring normative values of an animal, testing the response to a drug or a toxic substance or is monitoring food intake or locomotor activity: the time of day will have a significant impact upon the result.

It is well known that 24 h rhythms of animal and man are not caused by the cyclical environment but rather are generated endogenously. A mammal, transferred to an environment free of any time information (constant conditions) continues to exhibit a circa 24 h periodicity. Since the endogenously generated periodicity is unequal to exactly 24 h, it looses synchronization with the external 24 h period, generated by the rotation of the earth around its axis. In constant conditions the circa 24 h rhythms (= circadian rhythms [1]) are free-running with an individually distinct, very precise periodicity for at least more than hundred days [2], several years [3] and even several generations [4].

The suprachiasmatic nuclei (SCN) are considered to be the generators of the autonomous, circadian rhythms. The periodic environment is just synchronizing them, coupling phases of the endogenous rhythm to corresponding phases of the exogenous 24 h environment. The monosynaptic, retino-hypothalamic tract (RHT) transmits the LD-message from the retina to the SCN [5, 6]. The entrainment of endogenous rhythms with the environmental light-dark zeitgeber occurs by means of a phase-dependent response to light stimuli [7-9].

While the light-dark cycle is the most widely used and thus most important zeitgeber, during recent years evidence was obtained that a periodic feeding-fasting cycle, too, has zeitgeber capabilities. Before entering into details, it appears useful, however, to list the criteria, an external periodic variable has to meet in order to be zeitgeber:

a) It must entrain a circadian rhythm, free-running so far in otherwise constant conditions ("catching of the free-running rhythm").

b) When entrainment is completed, a stable phase relationship exists between the periodic environmental variable and the rhythm.

c) The circadian rhythm must be entrainable, within the limits of entrainment, even with a period length unequal to 24 h.

d) Terminating the zeitgeber and returning to constant conditions, the phase of the circadian rhythm is determined by the preceding zeitgeber.

e) As a rule, after termination a zeitgeber has an impact upon the length of the endogenous period (tau) for some time ("aftereffect" [10]).

Thus, while a zeitgeber affects the circadian oscillator system itself, an external, periodic environmental variable can directly influence the rhythm without affecting the oscillator system. This effect usually is referred to as "masking" [11-14]. Characteristics of masking are:

a) Its immediacy: without transients (part of) the rhythm concentrates around the exogenous periodic function at the moment of its imposition or phase-shift.

b) Although (part of) the rhythm is "in phase" with the exogenous periodic variable, the oscillator system continues to free-run, which may, but does not need to, be reflected by the overt rhythm.

c) After termination of the periodic variable the phase of the free-running rhythm is not set by the preceding schedule. Rather the rhythm "starts" at the phase, set by the free-running oscillator system. This phase can be obtained by forward extrapolation of the free-running rhythm before imposition of the masking factor [12, 14-16].

d) Tau of the free-running rhythm is not affected by the preceding schedule (no "aftereffect").

Periodically restricted food access (RF) significantly affects the circadian rhythms of endocrine [17-21] digestive [22-24] and behavioral rhythms [11, 13, 25-30].

As compared to the LD-zeitgeber a daily schedule of restricted food access, however, appears to affect the circadian oscillator system of different mammalian species in a rather specific way.

In the intact rat the majority of the activity rhythm obviously is not affected by periodic food access but continues to free-run with almost unaltered period length. A part of the rhythm, however, dissociates and couples to the beginning of food access at a positive phase angle difference (anticipatory activity) [12, 16, 31] exhibiting circadian characteristics [13, 31-35]. Terminating the RF schedule, the rhythm continues to free-run completely unaffected by the preceding RF regimen [12, 16, 36].

However, if the circadian oscillators in the SCN are destroyed, the animals thus being completely arrhythmic, a regular RF-regimen does restore circadian rhythmicity. The experimental evidence so far suggests that a feeding entrainable oscillator system (FEO) exists. This FEO system evidently resides outside the SCN [13, 14, 31-35, 37-41]. In the rat the FEO-system, probably consisting of two mutually coupled oscillators [41-44] is supposed to be coupled to the light entrainable oscillator system (LEO), the latter one being not entrainable by RF [45, 46]. Thus, there is strong evidence for the existence of a FEO-system in the rat, although in intact animals it is hardly apparent, probably due to the dominance of the light-entrainable oscillator system.

Other mammalian animal species are less thouroughly investigated. In intact squirrel monkeys, time restricted feeding does not entrain the activity rhythm of the animals [47, 15, 26]. In two marsupial species, the quoll (*Dasyurus viverrinus*) and the kowari (*Dasyuroides byrnei*) [48, 49] evidence was obtained for entrainment of at least a component of the circadian rhythm by restricted food access.

In the syrian hamster, running wheel activity is entrained by RF when the quantity of food is reduced for 30%, but not, when 100% is available for a certain amount of time [50]. In the inbred mouse, entrainment by restricted food access apparently depends from the genome of the respective strain: the circadian rhythm of locomotor activity is entrained in CS but not in C57BL/6J mice [51].

So far the situation on entrainment by periodic food access appears rather delicate. Since the experiments in rat, mouse, hamster and two marsupial species unequivocally indicate the existence of a FEO system in these species, it appears to be of general interest to investigate a plethora of FEO question, e.g. about the nerval and/or humoral and/or metabolic mechanisms of entrainment by a periodical feeding-fasting cycle, the quality of the signal, its transmission, the location of the oscillator system, its coupling and hierarchical position relative to the LEO system etc. For further approaches to these questions it appears advantageous to have an additional, adaequate model, an intact, unlesioned animal, exhibiting overt rhythms which obviously are entrained by periodic food access.

## Masking and entrainment by RF in the rabbit

As will be outlined below, the rabbit meets the criteria for a model, suited for further approaches on FEO. The critical experiment is depicted in Fig. 1: a circadian rhythm, first entrained with the LD zeitgeber and then free-running in continuous light conditions (LL, 7 lux) with a period length greater than 24 h, was exposed to a regular 4 h feeding and 20 h fasting cycle. After 70 days the RF schedule was terminated and the animal was fed *ad libitum* again for further 120 days. Then a 4 h food access cycle, which was advanced for 10 min every day, was imposed lasting for a total of 100 days. Finally the animal was fed *ad libitum*. Five behavioral functions were monitored (locomotor activity, hard faeces excretion, food box activity, water intake and urine excretion). Fig. 1a shows the original data of locomotor activity, Fig. 1b those of hard faeces excretion of a representative animal for a total of 572 days.

The free-running rhythm is interrupted at the moment of RF imposition. Whereas the rhythm of hard faeces excretion appears to be almost cut off by the imposition of RF, the rhythm of locomotor activity, is not as severely masked.

Two processes are evident:

a) *an immediate process of masking*: irrespective of the phase relation between free-running rhythm and newly inserted RF schedule the rhythms are completely reorganized within the first days of RF, the majority of events being concentrated around food access (Fig. 1, days 160-200).

b) *a phase dependent process of entrainment*: in addition to the masking effect, a process of entrainment is running. The time of entrainment significantly depends on the phase difference between

locomotor activity

hard faeces
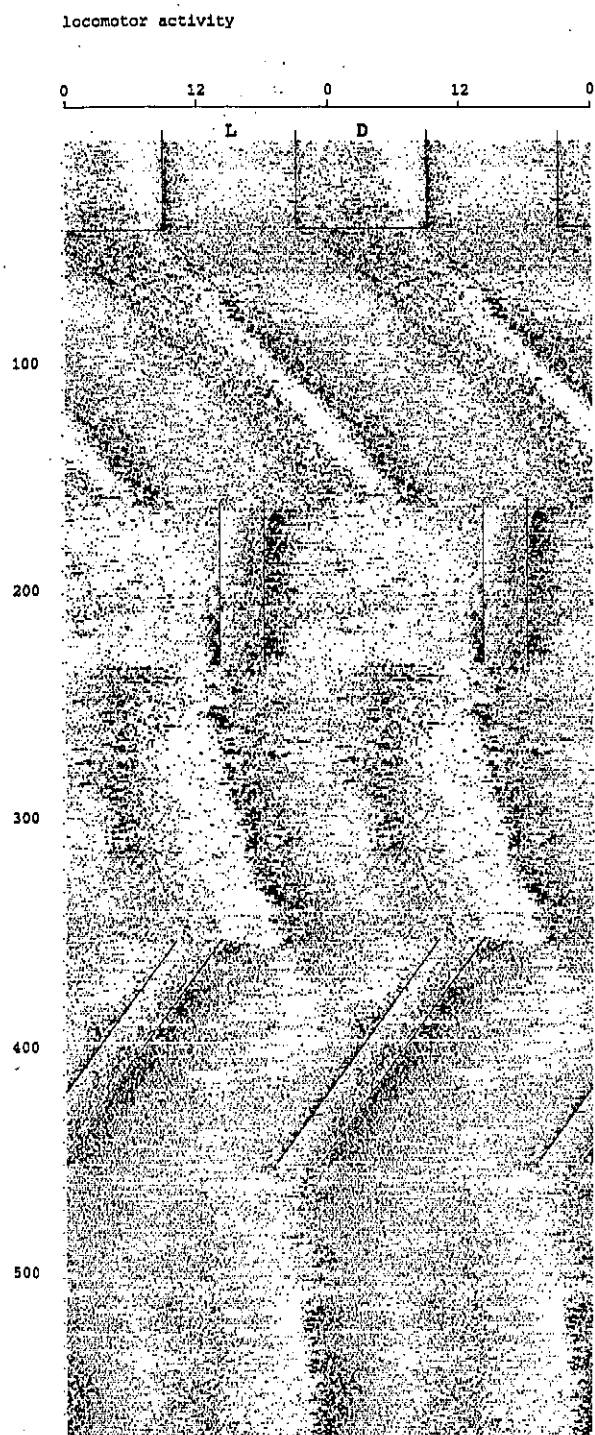
Fig. 1a. - Circadian bimodal rhythm of locomotor activity during LD 12:12 (day 1-40) and continuous light (LL) conditions (days 41-572). During LL two schedules of restricted food access are imposed (food access = 4 h): a first RF schedule with T_{RF} = 24 h and a second one with T_{RF} = 23 h 50 min (days 351-450). Entrainment with the first RF schedule is completed at day 50 of RF (experimental day 210). Entrainment with the second RF is completed around day 42 (experimental day 392).
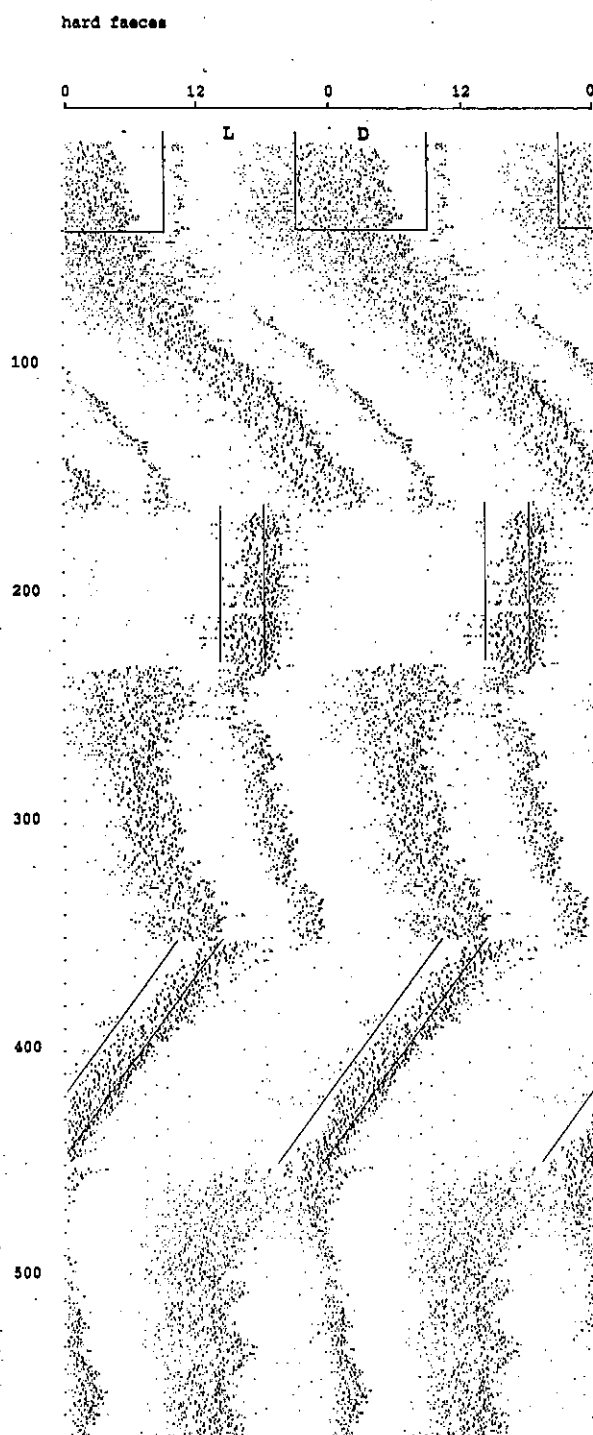
Fig. 1b. - Circadian, bimodal rhythm of hard faeces excretion during LD 12:12, continuous light (LL) conditions and two RF schedules. Same animal as in Fig. 1a. The rhythm of hard faeces excretion contains much less "noise" as compared to locomotor activity. By that it is well suited for demonstrating the asymmetry of the bimodal rhythm, the phase relationship between circadian rhythm and zeitgeber and the period length. Thus, the aftereffect of the rhythm following the termination of the zeitgeber, especially that with T_{RF} < 24 h is most obvious.

514
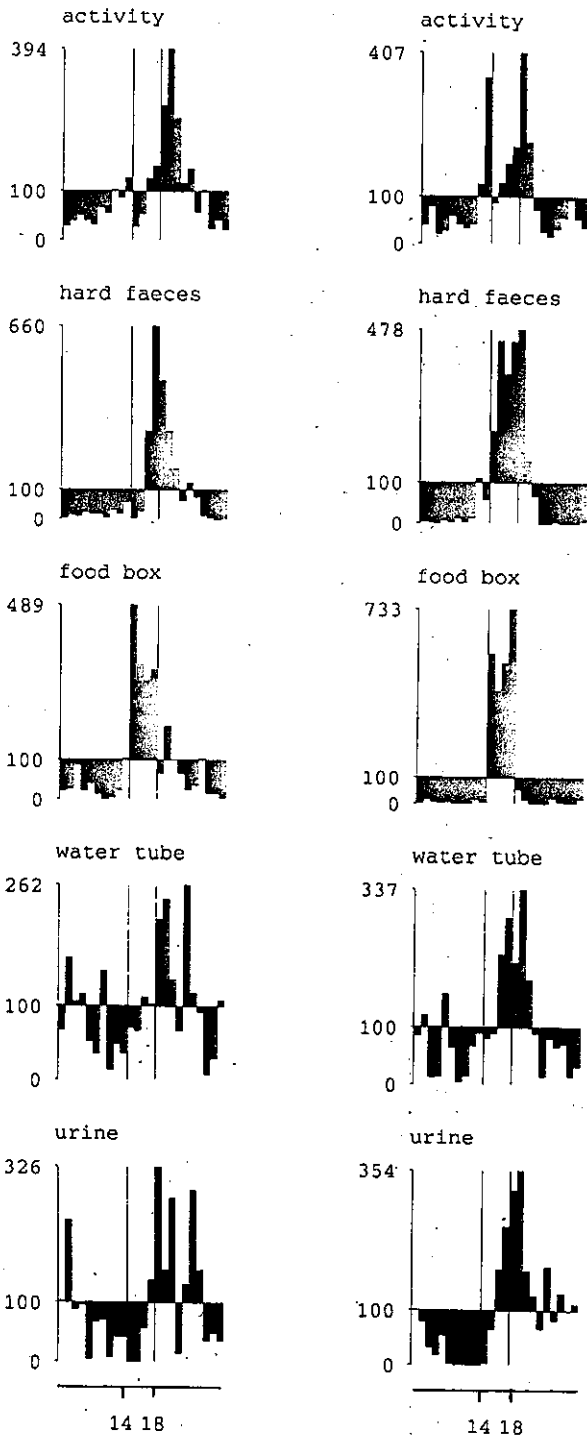
Fig. 2. - Average shape of five behavioral functions of a rabbit (same as in Fig. 1) during the first 10 days (left) and the last 10 days (right) of the first RF regimen (T_{RF} = 24 h). Ordinate: percental deviation of 60 min mean values from 24 h average (= 100%). Abscissa: time of the day, beginning at 04.00; time of food availability is indicated by two vertical lines. When masked (left), no significant componet of activity anticipates food availability; following entrainment anticipatory activity amounts to 19% of 24 h activity.

circadian rhythm and newly inserted RF regimen (coefficient of correlation r = 0.8304, n = 20 animals, p < 0.001). When entrainment is completed, a conspicuous activity component anticipates food availability for 60-90 min (Fig. 1a, Fig. 2). This component is established, when the forward extrapolated "morning component" of the free-running rhythm intersects the begin of food access. The component of anticipatory activity contains 25 ± 11% of 24 h activity (n = 10 animals). After complete entrainment (Fig. 1, day 210-230) the phase relationship between rhythm and zeitgeber is stable, no free-running components are detectable, neither visually nor by spectral analysis.

Terminating the schedule of restricted food access, an aftereffect of the preceding zeitgeber upon the circadian rhythm is evident fading out within 15-30 days of constant conditions. The circadian rhythm obviously starts to free-run from the phase of the preceding RF regimen. This is especially clearly demonstrated in functions of animals with a distinctly asymmetric bimodality of the rhythm as seen in Fig. 1b: since the circadian rhythm consists of a small "morning" and a larger "dark" component, it is obvious that the "morning" component of the free-running rhythm starts from the phase, set by the preceding food access. If the rhythm had been merely masked by RF it had started from a phase about 13 h later. In addition, the RF regimen of a zeitgeber-period T = 24 h exerts a significant aftereffect on the endogenous period: tau during the first 25 days amounts to 23.98 h and is significantly longer (tau = 24.08 h) thereafter.

The phenomena of immediate masking and gradual entrainment are almost identical when the period length of RF is shorter than 24 h (Fig. 1, days 351-450). The component of anticipatory activity, too, is established at the phase where the forwardly extrapolated "morning" component of the free-running rhythm intersects the begin of food access. The anticipatory component during T_{RF} < 24 h amounts to an average of 15 ± 7% (n = 15 animals). The impact of the zeitgeber period (T) is even more obvious at a T_{RF} shorter than 24 h: during the first 26 days after termination of RF the period length of the free-running rhythm is almost identical to T of the preceding zeitgeber (Fig. 1b, days 451-478). Then the rhythm is decomposed, the "morning" - component turning to tau > 24 h, the "dark" - component continuing for further 23 days with the period length of the preceding RF and then turning to a tau > 24 h, exhibiting a fluctuating periodicity for further 30-40 days.

These results obtained in intact rabbits indicate that the circadian oscillator system of the rabbit consists of at least two mutually coupled oscillators, a "morning" - oscillator and a "dark-oscillator". Apparently both are entrainable by a light-dark and by a feeding-fasting zeitgeber. Since RF was imposed during otherwise constant conditions the data so far do not provide an information, however,

locomotor activity
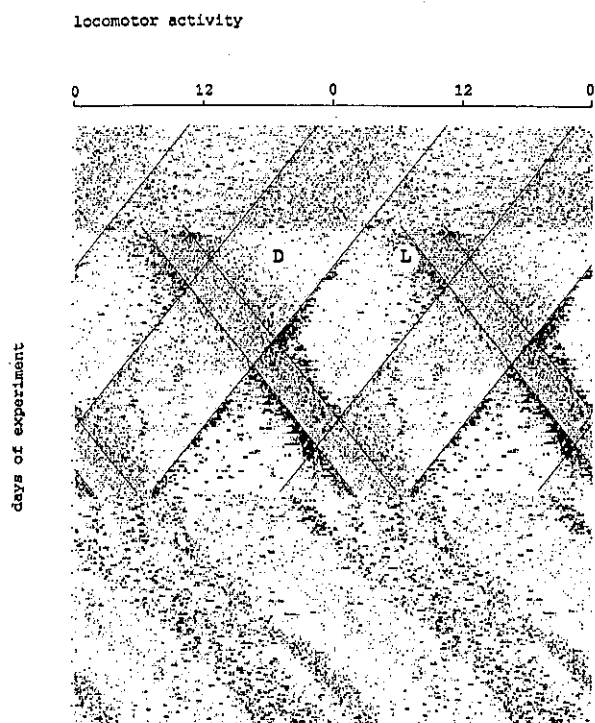
Fig. 3a. - Circadian rhythm of locomotor activity, first entrained with a light dark schedule of T_{LD} < 24 h and then exposed to an additional RF zeitgeber with T_{RF} > 24 h. Both zeitgebers have a significant impact upon the rhythm. After the simultaneous termination of the zeitgebers the rhythm free-runs with a period length approximating T of the preceding RF, not T of the LD schedule.

whether either oscillator is entrainable by the light-dark and the feeding fasting zeitgeber (one oscillator system, two inputs) or whether the circadian system of the rabbit consists of two oscillator systems, a light-dark entrainable and a feeding-fasting entrainable one (two oscillator systems with one input each).

One or two oscillator systems?

If two circadian oscillator systems are existing in the rabbit, a LD-entrainable and a RF-entrainable one, then a schedule of two conflicting zeitgebers, one running with a period longer, the other one with a period shorter than 24 h should have an impact upon the light-entrainable (part of the) rhythm (LER) and the feeding-entrainable (part of the) rhythm (FER). In other words: if part of the rhythm is entrained by either zeitgeber, this would be a striking evidence for the existence of a LEO- and a FEO-system in intact, unlesioned animals.

Fig. 3a shows the original data of a representative animal. The experiment resulted in at least four important points:

a) The shape of the rhythm during restricted food access taking place in the dark period differs

conspicuously from that of RF in L. Locomotor activity is more diffusely distributed around RF occurring in D, the component of anticipatory activity contains 16 ± 4% of 24 h activity (n = 5 animals, two repetitions) (Fig. 3b).

b) During restricted food access in L the component of anticipatory activity contains 27 ± 2%
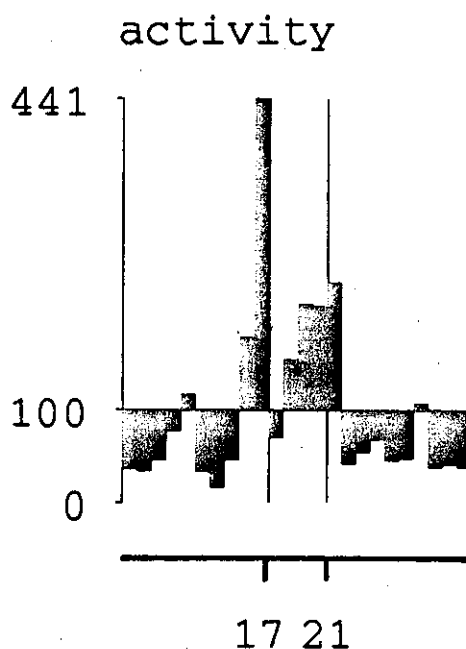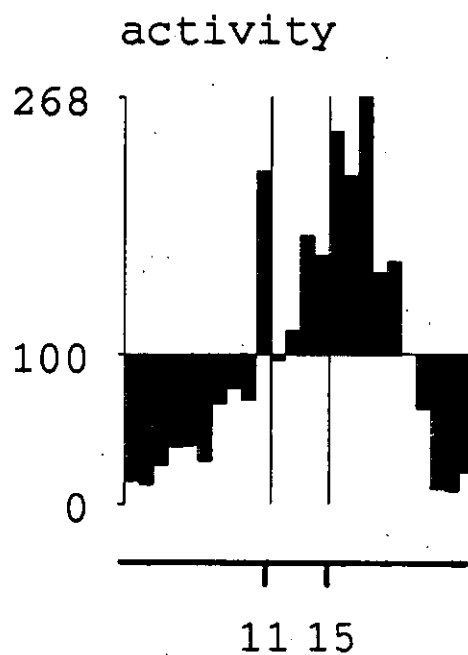
Fig. 3b. - Average shape of locomotor activity (=rabbit Fig. 3a) entrained with RF situated during the dark (left) and the light period (right); the data of 19 days at either schedule are calculated and plotted. Amount of anticipatory activity during RF in D: 9%, during RF in L: 26%.

of 24 h activity (n = 5 animals, two repetitions), it precedes the beginning of food access for 60-90 min (Fig. 3b).

c) An additional activity component ("morning" c., comprising 20 ± 7%) exists around the dark/light (D/L) transition. It precedes the D/L transition for up to 30 min. When this component approaches the end of food access, it merges into the activity component around the end of food access. The "morning" component consolidates again, when the phase angle difference between lights on and begin of food availability amounts to 4-6 h (about 15 days after the "lights on" had crossed the beginning of food availability).

d) At the simultaneous termination of both zeitgebers the period length of RF, not that of LD exerts a conspicuous aftereffect upon the period length of the circadian rhythm.

These effects of both zeitgebers upon locomotor activity are seen similarly in four other behavioral functions (hard faeces excretion, water intake, food box activity, urine excretion) indicating the common control of these functions by two different oscillator systems, a light entrainable and a feeding-fasting entrainable one. The mergence of the "morning"-component into the component of succeeding activity after food access and its reconsolidation 27-30 days thereafter indicates a close coupling between the LEO and the FEO system. Despite the conspicuous impact of the LD zeitgeber upon the circadian rhythm the RF zeitgeber evidently is dominant. This is documented by the phase of the free-running rhythm and, especially, by the conspicuous aftereffect of T_{RF} on tau after termination of RF. Experiments in which rabbits were exposed to simultaneous LD and RF zeitgebers of equal period length are corroborating this view. It, thus, appears that in the rabbit during *ad libitum* food access the light entrainable oscillator system controls circadian functions whereas during restricted food access the feeding entrainable oscillator system is playing the dominant role.

Biological significance of a feeding entrainable oscillator system in the rabbit

The nursing behavior of the rabbit differs from that of most other mammals. In animal house conditions as well as in the natural habitat the doe rabbit visits her litter once/24 h, nursing the pups for 3-5 min only and leaving them alone and without any care for the rest of the day [52-58]. During the limited nursing visit of the doe the pups can ingest a quantity of milk, amounting to 20-30% of their body weight. Since the rabbit pups during their first days of life, thus, are exposed to a natural cycle of restricted "food access", imposed by their mother, it was important to know whether the pups would anticipate nursing time in a similar way as seen in adult rabbits during artificial RF schedules.

As demonstrated in > 20 does, kept in our completely insulated "Chronolab", the doe is giving birth during her resting time, i.e. during the light period. The first nursing occurs 20-22 h after birth, during the last hours of the dark period. During the following days the nursing visit is advanced every day for an average of 30 ± 10 min, thus the doe shifts nursing to the first part of the dark = activity period. The nursing visit lasts 4 ± 1 min. The pups are anticipating the arrival of the doe by day 2-4 of life: 60-72 min before she enters the litter box, the activity of the pups increases, exceeding significantly the 24 h average (= 0%) for 40 – > 200% (Fig. 4). The anticipatory activation most probably neither is the result of direct signalling by the doe nor is the doe "called" by the pups. Rather anticipatory activity seems to be generated endogenously by a feeding entrainable oscillator system which is already functioning during the first days of life and is entrainable by restricted milk access to a zeitgeber period of T < 24 h. In favour of this hypothesis is the activity rhythm in litters of does, which occasionally splitted the nursing rhythm: while the additional, advanced nursing is not anticipated at all before day 3, the first nursing during D, which was delayed for about 2 1/2 h relative to nursing time the day before, is anticipated for > 120 min, the percentage amounting to 272% on day 12, 70% on day 13, 173% on day 14 and 153% on day 15 (Fig. 5). In favour of our entrainment hypothesis of anticipatory activity by nursing is the entrainability of anticipatory activity of the pups by a schedule of "timed" nursing: when the doe has restricted access to the litter box, e.g. every day at 09.00, then the anticipatory activity of the pups is entrained with the zeitgeber period of T = 24 h. The amount of anticipatory

activity pups

Fig. 4. - Rhythm of litter activity and nursing between the 7th and the 14th day of the pup's life. The data of litter activity are plotted standing on the line, the nursing visit (=presence) of the doe is plotted downwards. The 12 min averages 60-90 min before the doe entered the litter box exceeded the respective 24 h average (= 0% by: day 7: 65%; day 8: 195%; day 9: 213%; day 10: 71%; day 11: 148%; day 12: 44%; day 13: 179%; day 14: 201%.
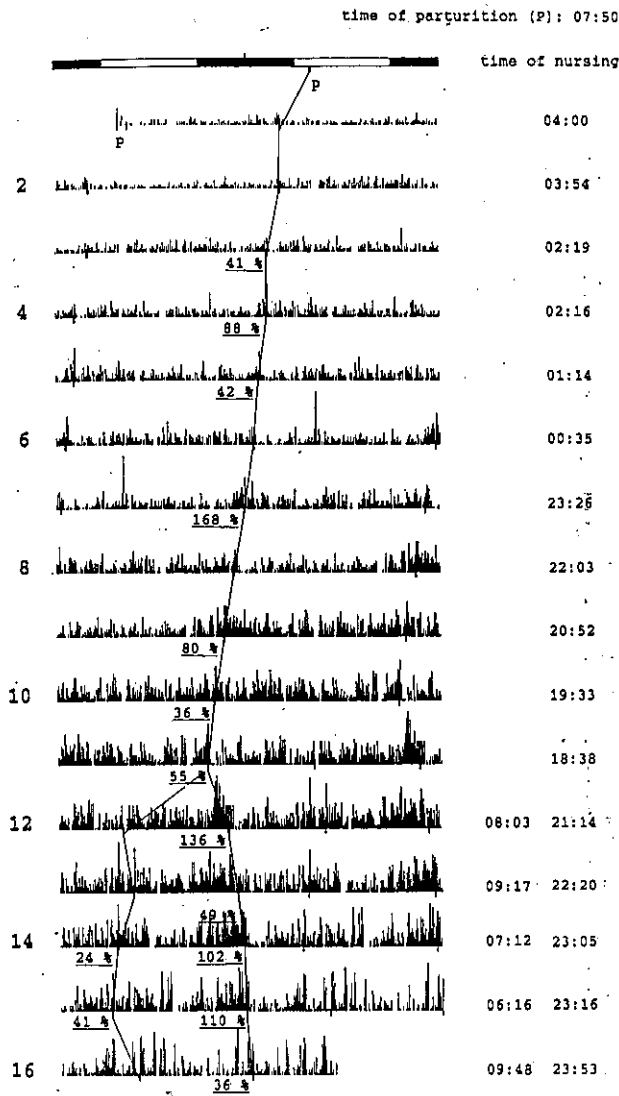
Fig. 5. - Rhythm of litter activity and nursing from birth to day 16 of the pup's life. A regular advance shift of nursing time occurs between days 1-11. The pups anticipate nursing time by significantly elevated activity 60-90 min prior to the doe's arrival. When the nursing rhythm was split on day 12, the advanced nursing time was not anticipated before the third nursing. Percentages indicate activity of 5 * 12 min bins, significantly elevated above the respective 24 h average (= 0%).

activity of the litters and the duration of nursing during this schedule is almost the same as during *ad libitum* nursing.

The rabbit is a predominantly nocturnally active animal [59]. As in other nocturnal animals [60-62], parturition predominantly occurs during the subjective resting = light period. The rabbit pup is born with closed eyelids, not able to discriminate between light and dark before day 7-8 of life [63, 64]. In addition, in the natural habitat it is born into a continuously dark burrow. In contrast to mouse, hamster and rat the doe has to visit her litters in a separate burrow, apart from her living area. It appears advantageous and perhaps even necessary for the doe to advance nursing time across the dark hours to the first part of D and thus to synchronize nursing with her main activity time. The pups, during their first days of life almost without hair and thermoregulatory incompetent, are huddled closely together, completely covered by nesting material. During the short presence time of the doe they usually ingest a quantity of milk, corresponding to 10-30% of their body mass. To be awake and out of the nest at the arrival of the doe, increases the chance of getting enough milk. Video films showed that the anticipatory activity consisted of uncovering from the nesting material and an additional, apparently non-specific component of activity. Thus, the ability to measure time and entrain it with a periodic environmental variable - nursing time - guarantees that the pups are at the right time at the right place and prepared for immediate suckling at the arrival of - doe. The endogenous and exogenous conditions - physiological inability to discriminate between L and D and, in the natural habitat, continuous darkness - makes a light entrainable oscillator system during this state of development useless and, during evolution, might have favoured the development and selection for an additional, feeding entrainable oscillator system. Follow-up experiments indicated that in the course of maturation of the animal the LEO system becomes dominant and takes over control on circadian behavioral functions around weaning, then entraining the circadian system with the light-dark zeitgeber.

REFERENCES

1. HALBERG, F. 1959. Physiologic 24 h periodicity in human beings and mice, the lighting regimen and daily routine. In: Photoperiodism and related phenomena in plants and animals. R.B. Withrow (Ed.). *Am. Assoc. Adv. Sci.* pp. 803-878.

2. JILGE, B. 1980. The effect of two different light intensities on spontaneous period and phase angle difference of caecotrophy-rhythm in the rabbit. *J. Interdiscipl. Cycle Res.* 11: 41-54.

3. RICHTER, C. 1968. Inherent twenty-four hour and lunar clocks of a primate - the squirrel monkey. *Comm. Behav. Biol.* 1: 305-332.

4. ASCHOFF, J. 1960. Exogenous and endogenous components in circadian rhythms. *Cold Spring Harbor Symp Quant. Biol.* **25**: 11-28.

5. MOORE, R.Y. 1972. Retinohypothalamic projections in mammals: a comparative study. *Brain Res.* **49**: 403-409.

6. MOORE, R.Y. & LENN, N.J. 1972. A retinohypothalamic projection in the rat. *J. Comp. Neurol.* **146**: 1-14.

7. DE COURSEY, P.J. 1960. Daily light sensitivity rhythm in a rodent. *Science* **131**: 33-35.

8. DE COURSEY, P.J. 1960. Phase control of activity in a rodent. *Cold Spring Harbor Symp. Quant. Biol.* **25**: 49-55.

9. DAAN, S. & PITTENDRIGH, C.S. 1976. A functional analysis of circadian pacemakers in nocturnal rodents II. The variability of phase response curves *J. Comp. Physiol.* **106**: 253-266.

10. PITTENDRIGH, C.S. & DAAN, S. 1976. A functional analysis of circadian pacemakers in nocturnal rodents: I. The stability and lability of spontaneous frequency. *J. Comp. Physiol.* **106**: 223-252.

11. ASCHOFF, J. 1986. Anticipation of a daily meal: a process of "learning due to entrainment". *Monitore Zool. Ital.* **20**: 195-219.

12. ASCHOFF, J., VON GOETZ, C. & HONMA, K.-I. 1983. Restricted feeding in rats: effects of varying feeding cycles. *Z. Tierpsychol.* **63**: 91-111.

13. BOULOS, Z., ROSENWASSER, A.M. & TERMAN, M. 1980. Feeding schedules and the circadian organization of behavior in the rat. *Behav. Brain Res.* **1**: 39-65.

14. BOULOS, Z. & TERMAN, M. 1980. Food availability and daily biological rhythms. *Neurosci. Biobehav. Rev.* **4**: 119-131.

15. ASCHOFF, J. & VON GOETZ, C. 1986. Effects of feeding cycles on circadian rhythms in squirrel monkeys *J. Biol. Rhythms* **1**: 267-276.

16. HONMA, K.-I., VON GOETZ, C. & ASCHOFF, J. 1983. Effects of restricted feeding on freerunning circadian rhythms in rats. *Physiol. Behav.* **30**: 905-913.

17. AHLERS, I., SMAJDA, B. & AHLERSOVA, E. 1988. Circadian rhythm of plasma and adrenal corticosterone in rats: effect of restricted feeding schedules. *Endocrinol. Exp.* **14**: 183-190.

18. HIRAI, T. 1992. The neuroendocrine regulation of plasma corticosterone rhythm in rat. *Hokkaido J. Med. Sci.* **67**: 12-16.

19. HONMA, K.-I., HONMA, S. & HIROSHIGE, T. 1984. Feeding-associated corticosterone peak in rats under various feeding cycles *Am. J. Physiol.* **246**: R721-R726.

20. HONMA, K.-I., HONMA, S., HIRAI, T., KATSUNO, Y. & HIROSHIGE, T. 1986. Food ingestion is more important to plasma corticosterone dynamics than water intake in rats under restricted daily feeding *Physiol. Behav.* **37**: 791-795.

21. KRIEGER, D.T. 1974. Food and water restriction shifts corticosterone temperature, activity and brain amine periodicity. *Endocrinology* **95**: 1195-1201.

22. FURUYA, S., SITREN, H.S., ZEIGEN, S., OFFORD, C.E. & STEVENSON, N.E. 1979. Alterations in the circadian rhythmicity of rat small intestinal functions. *J. Nutr.* **109**: 1962-1973.

23. SAITO, M., KATO, H. & SUDA, M. 1980. Circadian rhythm of intestinal disaccharidases of rats fed with adiurnal periodicity. *Am. J. Physiol.* **238**: G97-G101.

24. STEVENSON, N.R. & FIERSTEIN, J.S. 1974. Diurnal rhythms of intestinal enzymes and transport systems in the rat and the effect of restricted feeding on these rhythms. *Gastroenterology* **66**: 784-789.

25. ANIAS, J. 1991. Food anticipatory yawning rhythm in the rat. *Acta Neurobiol.* **51**: 97-105.

26. BOULOS, Z., FRIM, D.M., DEWEY, L.K. & MOORE-EDE, M.C. 1989. Effects of restricted feeding schedules on circadian organization of squirrel monkeys. *Physiol. Behav.* **45**: 507-515.

27. JILGE, B. 1987. Entrainment and masking of circadian rhythms of rabbits by restrictive feeding. In: *Chronobiology and chronomedicine*. G. Hildebrandt, R. Moog & F. Raschke (Eds). P. Lang, Frankfurt, Berlin, New York, Paris. pp. 140-146.

28. JILGE, B. 1992. Restricted feeding: a nonphotic zeitgeber in the rabbit. *Physiol. Behav.* **51**: 157-166.

29. JILGE, B., HÖRNICHE, H. & STÄHLE, H. 1987. Circadian rhythms of rabbits during restrictive feeding. *Am. J. Physiol.* **253**: R46-R54.

30. ROSENWASSER, A.M. & ADLER, N.T. 1986. Structure and function in circadian timing systems: evidence for multiple coupled oscillators. *Neurosci. Biobehav. Rev.* **10**: 431-448.

31. STEPHAN, F.K. 1986. Interaction between light- and feeding-entrainable circadian rhythms in the rat. *Physiol. Behav.* **38**: 127-133.

32. BOLLES, R.C. & STOKES, L.W. 1965. Rat's anticipation of diurnal and a-diurnal feeding. *J. Comp. Physiol. Psychol.* **60**: 290-294.

33. BOLLES, R.C. & MOOT, S.A. 1973. The rat's anticipation of two meals a day. *J. Comp. Physiol. Psychol.* **83**: 510-514.

34. STEPHAN, F.K. 1981. Limits of entrainment to periodic feeding in rats with suprachiasmatic lesions. *J. Comp. Physiol.* **143**: 401-410.

35. STEPHAN, F.K. 1986. Coupling between feeding- and light-entrainable circadian pacemakers in the rat. *Physiol. Behav.* **38**: 537-544.

36. GIBBS, F.P. 1979. Fixed interval feeding does not entrain the circadian pacemaker in blind rats. *Am. J. Physiol.* **236**: R249-R253.

37. CLARKE, J.D. & COLEMAN, G.J. 1986. Persistent meal-associated rhythms in SCN-lesioned rats. *Physiol. Behav.* **36**: 105-113.

38. COLEMAN, G.J., HARPER, S., CLARKE, J.D. & ARMSTRONG, S. 1982. Evidence for a separate meal-associated oscillator in the rat. *Physiol. Behav.* **29**: 107-115.

39. ROSENWASSER, A.M., PELCHAT, R.J. & ADLER, N.T. 1984. Memory of feeding time: possible dependence on coupled circadian oscillators. *Physiol. Behav.* **32**: 25-30.

40. STEPHAN, F.K., SWANN, J.M. & SISK, C.L. 1979. Anticipation of 24 hour feeding schedules in rats with lesions of the suprachiasmatic nuclei. *Behav. Neural Biol.* **25**: 346-363.

41. STEPHAN, F.K., SWANN, J.M. & SISK, C.L. 1979. Entrainment of circadian rhythms by feeding schedules in rats with suprachiasmatic lesions. *Neural Biol.* **25**: 545-554.

42. MISTLBERGER, R.E., HOUPT, T.A. & MOORE-EDE, M.C. 1990. Characteristics of food-entrained circadian rhythms in rats during long-term exposure to constant light. *Chronobiol. Int.* **7**: 383-391.

43. OTTENWELLER, J.E., TRAPP, W.N. & NATELSON, B.N. 1990. Phase-shifting the light-dark cycle resets the food-entrainable circadian pacemaker. *Am. J. Physiol.* **258**: R994-R1000.

44. STEPHAN, F.K. & BECKER, G. 1989. Entrainment of anticipatory activity to various durations of food access. *Physiol. Behav.* **46**: 731-742.

45. INOUYE, S.T. 1982. Restricted daily feeding does not entrain rhythms of the suprachiasmatic nucleus in the rat. *Brain Res.* **232**: 194-199.

46. SHIBATA, S., LIOU, S.Y., UEKI, S. & OOMURA, Y. 1983. Effects of restricted feeding on single neuron activity of suprachiasmatic neurons in rat hypothalamic slice preparation. *Physiol. Behav.* **31**: 523-528.

47. FRIM, D.M., BOULOS, Z. & MOORE-EDE, M.C. 1984. Restricted but unsignalled daily food availability synchronizes anticipatory behavior but fails to entrain other circadian rhythms *Soc. Neurosci.* **10**: 504.

48. KENNEDY, G.A., COLEMAN, G.J. & ARMSTRONG, S.M. 1990. The effect of restricted feeding on the wheel-running activity rhythms of the predatory marsupial Dasyurus viverrinus. *J. Comp. Physiol.* **166**: 607-618.

49. KENNEDY, G.A., COLEMAN, G.J. & ARMSTRONG, S.M. 1991. Restricted feeding entrains circadian wheel-running activity of the kowari. *Am. J. Physiol.* **261**: R819-R827.

50. ABE, H., KIDA, M. & MANO, T. 1989. Effects of periodic restricted feeding on circadian activity rhythms in the golden hamster. *Environ. Med.* **33**: 99-102.

51. ABE, H., KIDA, M., TSULI, K. & MANO, T. 1989. Feeding cycles entrain circadian rhythms of locomotor activity in CS mice but not in C57BL-6J mice. *Physiol. Behav.* **45**: 397-402.

52. BROEKHUIZEN, S., BOUMAN, E. & WENT, W. 1986. Variation in timing of nursing in the brown hare (Lepus europaeus) and the European rabbit (Oryctolagus cuniculus). *Mammal Rev.* **16**: 139-144.

53. HUDSON, R. & DISTEL, H. 1982. The pattern of behaviour of rabbit pups in the nest. *Behaviour* **79**: 255-271.

54. HUDSON, R. & DISTEL, H. 1989. Temporal pattern of suckling in rabbit pups: a model of circadian synchrony between mother and young. In: *Research in perinatal medicine*. Vol. IX: Development of circadian rhythmicity and photoperiodism in mammals. S.M. Reppert (Ed.). Perinatology Press Ithaca, New York, pp. 83-102.

55. LINCOLN, D.W. 1974. Suckling: a time constant in the nursing behaviour of the rabbit. *Physiol. Behav.* **13**: 711-714.

56. MYKYTOWICZ, R. & ROWLEY, I. 1958. Continuous observations of the activity of the wild rabbit (Oryctolagus Cuniculus L.) during 24 hour periods. *CSIRO Wildl. Res.* **3**: 26-31.

57. VENGE, O. 1963. The influence of nursing behaviour and milk production on early growth in rabbits. *Anim. Behav.* **11**: 500-506.

58. ZARROW, M.X., DENENBERG, V.H. & ANDERSON, C.O. 1965. Rabbit: frequency of suckling in the pup. *Science* **150**: 1835-1836.

59. JILGE, B. 1991. The rabbit: a diurnal or a nocturnal animal? *J. Exp. Anim. Sci.* **34**: 170-183.

60. GATTERMANN, R. 1983. Die zirkadiane Verteilung der Geburten beim Goldhamster. *Z. Versuchstierk.* **25**: 293-295.

61. LINCOLN, D.W. & PORTER, D.G. 1976. Timing of the photoperiod and the hour of birth in rats. *Nature* **260**: 780-781.

62. BOSC, M.J. 1990. Photoperiodic regulation of the time of birth in rats: involvement of circadian endogenous mechanisms. *Physiol. Behav.* **48**: 441-446.

63. RIPISARDI, S.C., CHOW, K.L. & MATHERS, L.H. 1975. Ontogenesis of receptive field characteristics in the dorsal lateral geniculate nucleus of the rabbit. *Exp. Brain Res.* **22**: 295-305.

64. STEWART, D.L., CHOW, K.L. & MASLAND, R.H. 1971. Receptive field characteristics of lateral geniculate neurons in the rabbit. *J. Neurophysiol.* **34**: 139-147.

65. JILGE, B. & STÄHLE, H. 1993. Restricted food access and light-dark: impact of conflicting zeitgebers upon circadian rhythms of the rabbit. *Am J. Physiol.* **264**: 2708-2715.