

Entrainment of Methamphetamine-Induced Locomotor Activity Rhythm to Feeding Cycles in SCN-Lesioned Rats

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HONMA, S., N. KANEMATSU AND K.-I. HONMA. *Entrainment of methamphetamine-induced locomotor activity rhythm to feeding cycles in SCN-lesioned rats.* *PHYSIOL BEHAV* 52(5) 843-850, 1992.—Suprachiasmatic nuclei (SCN)-lesioned rats, showing a locomotor activity rhythm with a circadian period by chronic methamphetamine treatment, were subjected to the periodic food restriction (RF) of 4 h per every 27 h and 24 h. All rats were phase set by the feeding schedule of both 24-h and 27-h periods. Phase angle differences between the activity onset and food presentation were more positive under the RF with a period of 27 h than that of 24 h. Methamphetamine-induced locomotor rhythm showed a stable entrainment to RF of the 27-h period in all rats. Under the RF of the 24-h period, on the other hand, some rats showed circadian rhythms, i.e., an activity band appeared at every second food presentation. After the termination of feeding schedule, the locomotor rhythm started to free-run from the phase set by the previous feeding schedule in all rats examined. Methamphetamine-induced locomotor rhythm was shown to be entrained by the RF with a predictable manner of an oscillation theory.

Methamphetamine Food-entrainable rhythm Circadian rhythm Suprachiasmatic nucleus Locomotor activity
Restricted feeding

THE suprachiasmatic nucleus of the hypothalamus (SCN) is an essential structure for the circadian pacemaking system in rodents (15). Destruction of the SCN results in total and irreversible loss of the overt circadian rhythms (20,27). However, two rhythms have been observed so far in SCN-lesioned rats that have a period within a circadian domain. One is food-entrainable rhythm, which entrains to restricted feeding schedule (RF). When food availability is limited to a certain time of the day, rats show prefeeding peaks in locomotor activity, plasma corticosterone level, and many other physiological functions (1,2,6,7). The other is methamphetamine (MAP)-induced rhythm. By chronic treatment with MAP, a robust rhythm with a circadian period appeared in SCN-lesioned rats (9). The two rhythms did not entrain to the light cycle and are considered to be driven by an intrinsic oscillation(s) (3,11). Furthermore, MAP-induced locomotor rhythm was phase set by the RF with a period of 24 h (12). The two SCN-independent rhythms seems to have much in common. Rusak and Bina interpreted that the MAP-induced rhythm was the continuous expression of the food-entrainable rhythm under the specific condition of drug treatment (24). However, dissimilarities were also pointed out between them. A marked difference is that the food-entrainable rhythm showed a positive phase angle to the periodic feeding throughout its range of entrainment (28), but the MAP-induced rhythm showed a negative phase angle under the RF of the 24-h period (12). In this experiment, SCN-

lesioned rats that showed locomotor rhythms with a stable circadian period by chronic methamphetamine treatment were subjected to RF of two different periodicities, 27 h and 24 h, which are longer and shorter than the mean period of the MAP-induced rhythm, respectively. Food entrainment of the MAP-induced rhythm and its relation to the food-entrainable rhythms are discussed.

METHOD

Animals

Wistar female rats were used. They were reared in our animal quarters where environmental conditions were controlled: light (LD 12:12 h, light on at 0600 h), temperature ($22 \pm 1^\circ\text{C}$), and humidity ($60 \pm 5\%$). Light intensity at the surface of the rat cages was about 100 lx. Rats had free access to rat chow (Oriental Yeast Co.) and water, unless otherwise stated. After the SCN lesion, rats were moved to the experimental room where the environmental conditions were the same as those in the animal quarters and housed individually in a polycarbonate cage ($36 \times 30 \times 17$ cm).

Surgical Procedure

At 3 months of age, electrolytic lesions were made stereotactically in the bilateral SCN under pentobarbital anesthesia, by

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passing a 1.5 mA DC into each nucleus for 20 s through a stainless steel electrode of 0.5 mm in diameter with an uninsulated tip of 0.1 mm in length (14).

Locomotor Activity

Spontaneous locomotor activity was measured by an infrared sensor system that senses the light from 6 to 15 μm wavelength, which corresponds to the thermal radiation of an animal in a cage (25). The time constant was set to 8 ms and the activity counts were calibrated by an Animex III (Shimadzu). Movements of an animal were digitized and fed into a NEC PC9801 computer every 15 min.

Experimental Procedure

The SCN-lesioned rats that showed no circadian rhythms in the locomotor activity for 2 months after the operation were treated with MAP. D-Methamphetamine hydrochloride (MAP, Dainippon) treatment was done by dissolving it in drinking water at a concentration of 0.005%. The MAP solution was freshly prepared every 2 to 3 days. Rats had free access to a bottle containing MAP solution under RF schedule as well as under ad lib feeding. Seven SCN-lesioned rats (rats No. 1804, 1806, 1814, 1819, 1820, 1822, 1823) were used in the present experiment, which showed a robust locomotor rhythm with a regular circadian period by chronic MAP treatment. Two months after the start of MAP treatment, a periodic food restriction schedule (RF) was imposed on the rats by restricting free access to food to 4 h per 27 h ($T = 27$ h). The RF with a 27-h period was continued for 14 cycles. Then rats were returned to ad lib feeding. After the 4 weeks of ad lib feeding, the same rats were subjected to RF with a 24-h period by restricting free access to food for 4 h, from 1000 to 1400 ($T = 24$ h). The RF with a 24-h period was continued for 10 to 16 days. Thereafter, all rats were fed ad lib again. The MAP treatment was continued for 4 more weeks. Measurement of locomotor activity was continued 3 additional weeks after the termination of MAP treatment.

TABLE I
PERIODS OF LOCOMOTOR ACTIVITY (h) UNDER THREE
AD LIB FEEDING CONDITIONS*

Rat No.	Before RF	Between RFs	After RF
1804	25.9	27.6	28.1
1806	25.7	26.4	28.5
1814	25.6	27.2	27.3
1819	24.5	26.4	27.8
1820	26.5	27.4	28.6
1822	26.2	27.0	29.2
1823	25.0	27.2	27.4
Mean \pm SE	25.6 \pm 0.3	26.9 \pm 0.1†	28.0 \pm 0.3‡

* Before the RF of a 27-h period (before RF), between two RF schedules (between RFs), and after the RF of a 24-h period (after RF).

†‡ $p < 0.01$ vs. †period before RF and ‡period between RFs, respectively.

Statistics

A chi-square periodogram combined with an analysis of variance was used to calculate periods of locomotor activity during MAP treatment and to evaluate a loss of the circadian rhythmicity in the SCN-lesioned rats before and after the MAP treatment (26). Activity records of the last 10 days of each experimental condition were used for the calculation of periodicity. The activity onset was designated as the beginning of an activity band that continued more than 4 h without rest. The criterion was set because SCN-lesioned rats showed short activity bouts of 2 to 3 h before and after the MAP treatment. Phase angle differences between the activity onset and food presentation were calculated using the activity records of the last 10 cycles of each RF schedule. In rats that showed circadian rhythms, a difference between an activity onset and the nearest feeding time was designated as the phase angle difference. Wilcoxon test was used

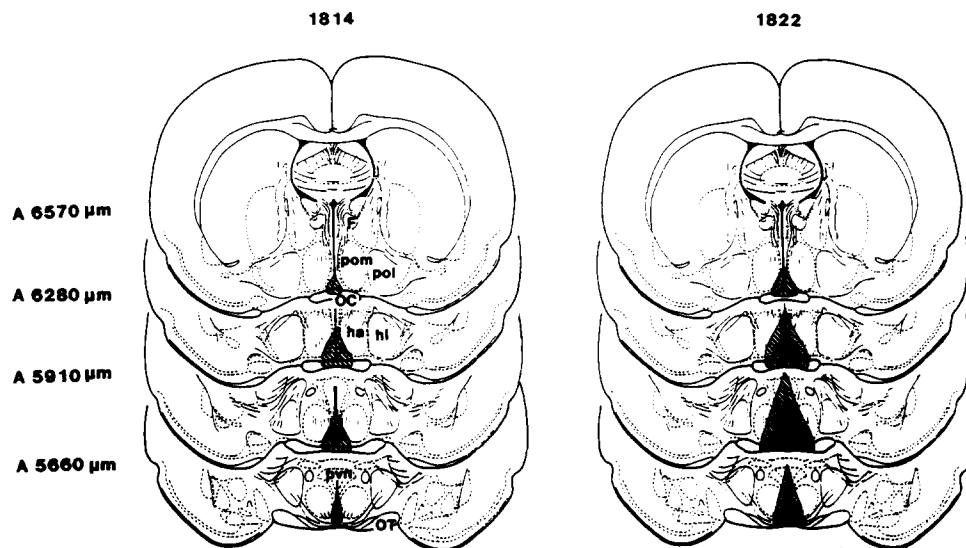


FIG. 1. The extent of the smallest (1814) and largest (1822) lesions (shaded areas) on the frontal planes of the anterior-posterior level from A 6570 to 5660 μm according to the atlas of König and Klippel (18). F, fornix; ha, anterior hypothalamic nucleus; hl, lateral hypothalamic nucleus; OC, optic chiasm; OT, optic tract; pol, lateral preoptic nucleus; pom, medial preoptic nucleus; pvn, paraventricular nucleus.

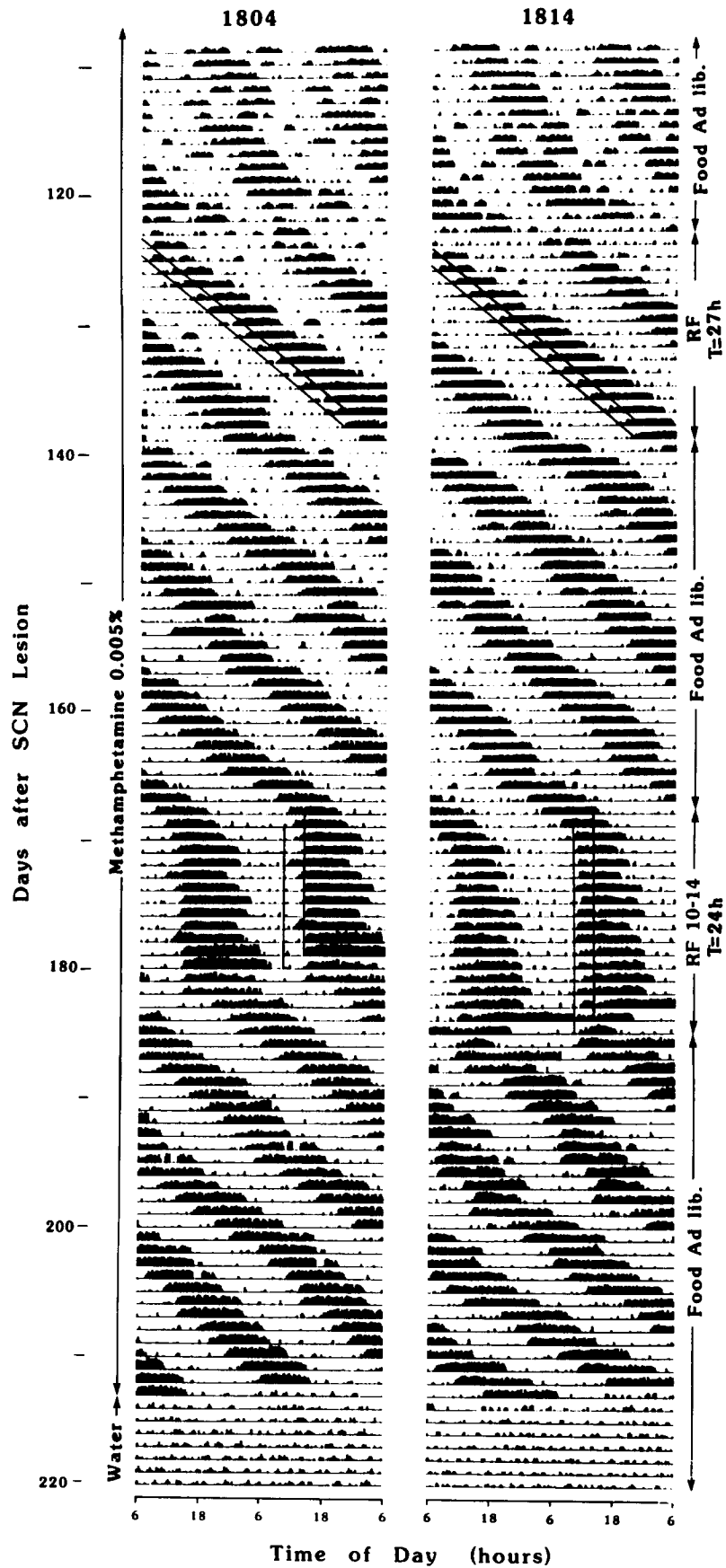


FIG. 2. Double-plotted locomotor activity records of two representative rats (1804 and 1814) before, during, and after the two RF schedules of a 27-h period ($T = 27$ h) and a 24-h period ($T = 24$ h). Activity was expressed in histograms of activity counts per 15 min; full scale indicates 1000 counts. Two parallel lines in the octogram indicate the time of food presentation. Rat 1804 showed a short activity time on the 153rd day and the phase advance of the activity onset on the next day due to the emptiness and replacement of MAP solution, respectively. This accident did not affect the locomotor rhythm of the following days.

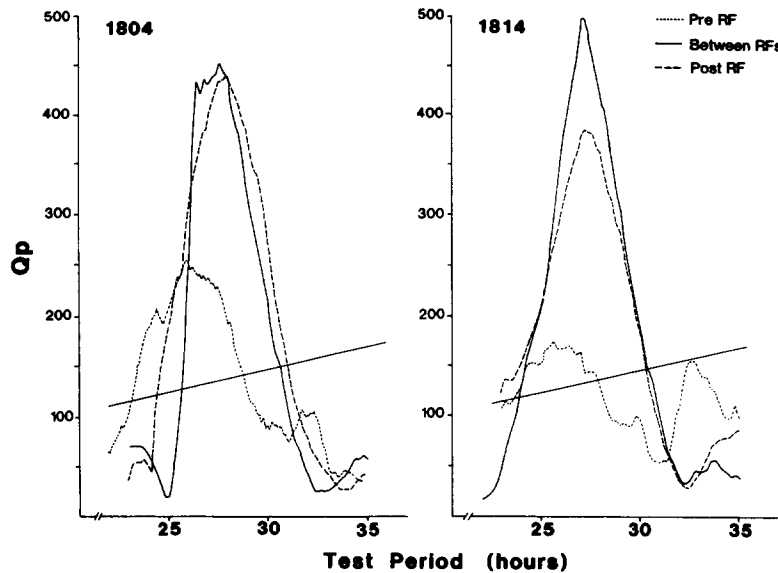


FIG. 3. Periods of locomotor activity rhythm in two representative rats (1804 and 1814) under three ad lib feeding conditions: before, between, and after the two RFs, analyzed by chi-square periodogram. Oblique lines represent a significant level of $p = 0.01$.

to compare the activity period, food and MAP intakes between the two schedules.

Histological Examination

At the end of the experiment, all the SCN-lesioned rats were deeply anesthetized with ether and perfused intracardially with saline followed by 10% formalin solution. Brains were fixed in 10% formalin solution at least 1 week. Frontal sections of the paraffin-embedded brains were cut serially throughout the lesioned areas and stained with luxolfast blue and cresyl violet.

RESULTS

SCN Lesions

Bilateral SCN were totally lesioned in all rats examined. In addition to the SCN, a part of the optic chiasm adjacent to the SCN and dorsomedial portion of the preoptic area were lesioned to various extent. In rats 1804, 1806, 1819, and 1822, the lesion was limited to the SCN and adjacent hypothalamic areas. The lesion extended to the ventrolateral part of the anterior hypothalamic nucleus, the dorsal part of periventricular nucleus, and the retrochiasmatic area in 1814, 1820, and 1823. However, the lateral preoptic area, paraventricular nucleus, ventromedial nucleus, and arcuate nucleus were intact. The largest and smallest lesions are schematically shown in Fig. 1.

Locomotor Activity Rhythms Under Ad Lib Feeding

Before the start of MAP treatment, all rats showed small activity bouts scattered throughout the 24 h and no circadian periodicity was calculated in their locomotor activities even under the LD cycles. By MAP treatment, the duration and amplification of each activity bout increased and coalesced, as reported previously (9), and the circadian periodicity appeared in the spontaneous locomotor activity observed under three ad lib feeding conditions: before, between, and after the two RF schedules. During the first 2 months, all rats showed locomotor

rhythms with a circadian period that ranged from 24.5 to 26.5 h. The activity period was significantly elongated after each RF session. The activity period became closer to 27 h in all rats after the 27-h schedule. On the other hand, the period became even longer than those before the RF after the 24-h schedule.

Figures 2 and 3 illustrate the actographs of two representative rats for 4 months of experiment and the results of period analyses of locomotor activity records under three ad lib feeding conditions, respectively. The activity rhythms, which were rather sloppy before the RF with the 27-h period, became robust after the RF. The periodogram analyses also revealed periods with higher peaks after the RF in all rats examined (Fig. 3).

After the termination of MAP treatment, the circadian activity rhythms disappeared in all rats and activity level decreased. Short activity bouts of 1- to 2-h length were scattered throughout the 24 h (Fig. 2). Period analyses revealed no significant periodicity within the circadian domain.

Effects of Periodic Food Restriction of 27-h and 24-h Periods

Activity rhythm phase set by the RF with a period of 27 h soon after the start of the schedule. The period analyses revealed a prominent peak at 27 h in all rats. Transients were not clearly observed. The phase relations between the time of activity onset and food presentation are shown in Figs. 2, 4, and 5. Table 2 summarizes the mean phase angle differences under the 27-h and 24-h feeding schedules. Under the 27-h schedule, the activity onset advanced to the time of food presentation. The activity time of each rat was relatively constant. After the termination of the RF, the activity rhythm started to free-run from the phase set by the prior RF (Fig. 2).

Under the RF with a period of 24 h, the activity rhythms were set by the schedule in all rats. The period analyses revealed 24-h periodicity with high significance. The phase angle differences between the food presentation and the activity onset became more negative than those under the 27-h schedule in all rats. The change in the phase angle difference was statistically significant between the two RFs. In individual rats, the change

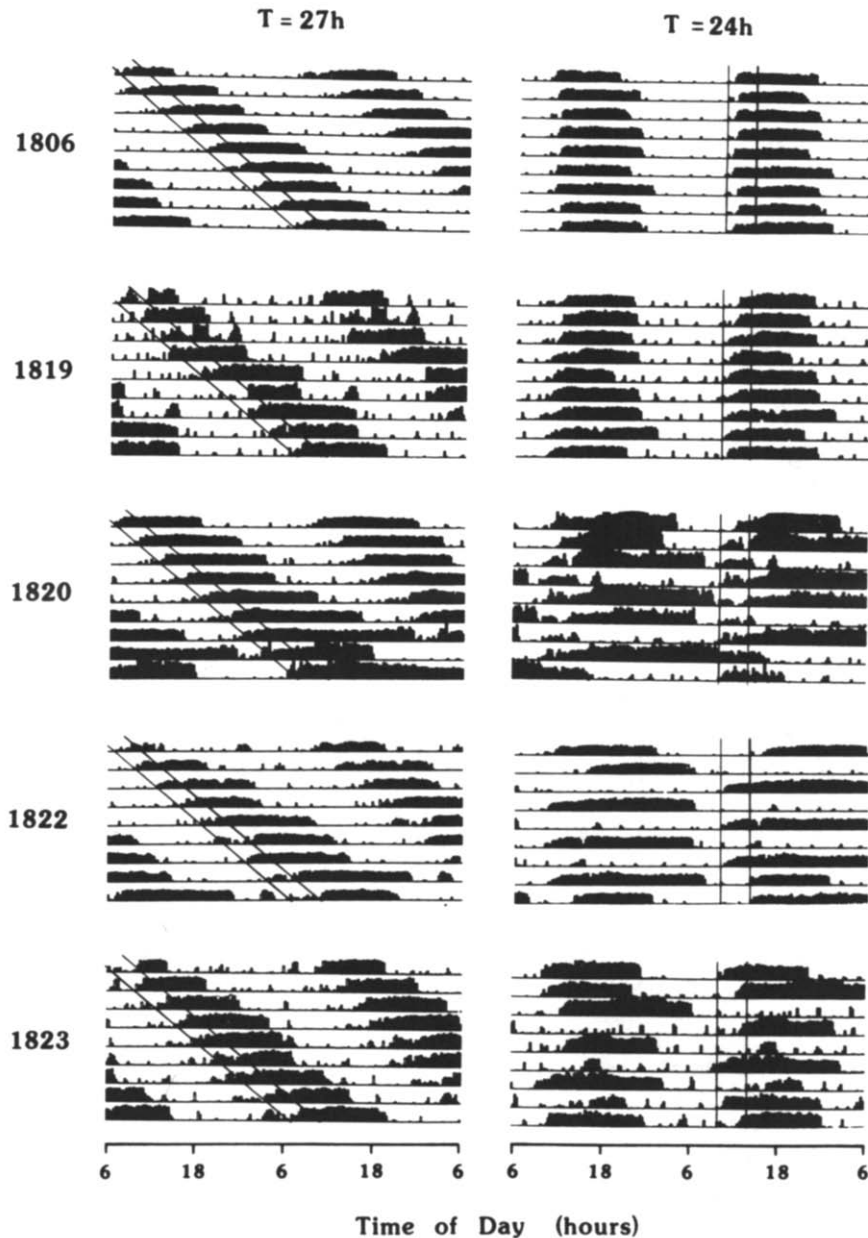


FIG. 4. Double-plotted locomotor activity records of five rats, during RF $T = 27$ h and $T = 24$ h. For the details, see the legend of Fig. 2.

was almost negligible in two rats (1814 and 1819) and significantly large in the remaining five.

The phase relation between the food presentation and activity onset was less stable under the 24-h schedule than under the 27-h schedule. Activity time also fluctuated. Three rats (1820, 1822, 1823) showed the circadian (about 48 h) activity rhythm, i.e., activity bands appeared every other feeding time, during the course of the 24-h schedule (Fig. 4). After the RF with a 24-h period, activity rhythm started to free-run again from the phase set by the prior RF (Fig. 2).

Changes in MAP Intake

The MAP intake in each experimental condition is shown in Table 3. The mean MAP intake was significantly lower before

the RF than for any other condition. Significant difference were not observed among the other four experimental conditions: under the two RFs, and before and after the RF with a 24-h period. The MAP intake during the RF schedules was not significantly different from those after the RFs.

DISCUSSION

The major difference between the two SCN-independent circadian oscillations, the food-entrainable and MAP-induced oscillations, is the difference in the phase relations between the activity onset and the meal time. The phase angle difference is positive throughout its range of entrainment for the former (28) and negative under the 24-h schedule for the latter (12). In our previous experiment, we observed changes in the phase angle

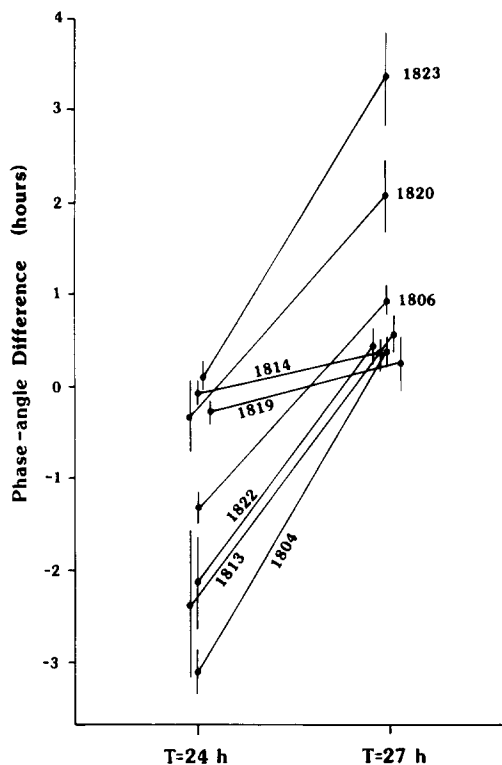


FIG. 5. Phase angle difference between the time of food presentation and activity onset under the two RFs of different T. Mean \pm SE of 10 consecutive cycles.

difference not by changing the period of zeitgeber but by manipulating underlying MAP-induced rhythm. In the present experiment, we observed changes in the phase angle differences under two periods of zeitgeber. The present results confirmed our previous observation of phase setting and a negative phase angle difference of MAP-induced locomotor rhythm by RF with a 24-h period (12). In addition, the present results clearly showed that the phase angle difference changed systematically under the RF of two different Ts, more positive under the 27-h schedule than the 24-h schedule. The period of the external zeitgeber was longer than the period of MAP-induced rhythm before imposing RF of 27 h. The mean phase angle difference (1.1 h) was much smaller than that of food-entrainable wheel-running and plasma corticosterone rhythms reported so far (1). The phase angle difference of MAP-induced locomotor rhythm was changed by the imposed period of food restriction (T) in a predicted manner from its endogenous periodicity. The phase angle was positive when the period of MAP-induced rhythm (τ) was shorter than T (27-h schedule), and it became negative when the τ was longer than T (24-h schedule) (23). On the other hand, the food-entrainable rhythm of both wheel-running and plasma corticosterone rhythms showed positive phase angle to the meal time, and the longer the T of feeding cycle, the more positive the phase angle became (1,2,7). Stephan reported that stable entrainment was obtained from 23 to 29 h of feeding schedules (28). Although it is difficult to measure the free-running period of the food-entrainable rhythm, it must be shorter than 23 h, according to an oscillation theory (23). In that experiment, the rhythm was not more entrained to the feeding schedule of the period shorter than 22 h. The results suggest that the two SCN-

independent oscillations are different in the entraining mechanisms.

Entrainment seemed to be more stable when the phase angle difference between the activity onset and the meal time was smaller. The day-to-day variations became larger as the phase angle difference became larger, regardless of the direction. Under the 27-h schedule, all rats fully entrained to the imposed zeitgeber; however, three out of seven rats showed circadian rhythm under the 24-h schedule. Fluctuations of the onset phase of activity and of length of activity time also suggest that a period of 24 h is close to the limit of entrainment. The periods under ad lib feeding, both before and after the 24-h schedule, were much closer to 24 h than to 48 h in these rats. Therefore, it seems difficult to explain the circadian rhythm as a result of the entrainment by frequency demultiplication (23).

After the RF, the period of MAP-induced rhythm became longer. Periods became close to the period of imposed zeitgeber in the case of the 27-h schedule, which may suggest the aftereffects of the oscillation (22). After the 24-h schedule, on the other hand, periods of locomotor rhythm became even longer than those before the RF. The activity rhythm that had been rather sloppy before the RF became robust after the RF. The phenomenon can be expected if the system was composed of multiple circadian oscillations that had been loosely coupled, and increased its precision in oscillation by a tighter coupling through entrainment (4).

Another difference, observed so far between the food-entrainable and MAP-induced rhythms, is the neural activity rhythm of the SCN. Multiple-unit activity recorded from the SCN showed robust circadian fluctuation that was not affected by the RF (16). But MAP treatment phase delayed the multiple-unit activity rhythm in relation to the LD cycle as it phase delayed the locomotor rhythm (21). Because the multiple-unit activity is one of the overt functions of the circadian oscillator, the results suggest that the MAP-induced oscillation was expressed at the level of neural activity of the SCN while the food-entrainable oscillation was not. Similarly, the MAP-induced locomotor rhythm interacted with the light-entrainable rhythm, which resulted in a relative coordination (8), while the anticipatory locomotor activity was almost independently expressed in rats under RF (6).

Similarities between the two rhythms are abundant: the SCN-independence, the circadian periodicity, the unentrainability to the light, the entrainability to the feeding cycle (9,3,28,29), the lack of the rhythm expression in the pineal melatonin (5,14), the negative energy balance (3,7,19), and probable involvement

TABLE 2
PHASE ANGLE DIFFERENCES BETWEEN THE ACTIVITY ONSET AND THE TIME OF FOOD PRESENTATION (h)

Rat No.	RF T = 27 h	RF T = 24 h
1804	0.38 \pm 0.17	-3.10 \pm 0.26
1806	0.92 \pm 0.16	-1.31 \pm 0.19
1814	0.36 \pm 0.18	-0.05 \pm 0.16
1819	0.23 \pm 0.37	-0.27 \pm 0.65
1820	2.03 \pm 0.40	-0.33 \pm 0.42
1822	0.43 \pm 0.22	-2.17 \pm 0.65
1823	3.32 \pm 0.64	0.10 \pm 0.08
Mean \pm SE	1.10 \pm 0.44	-1.01 \pm 0.46

Numbers are means \pm SE of 10 consecutive cycles for each rat and of seven rats for the group means.

TABLE 3
AMOUNT OF MAP INTAKE BEFORE, DURING, AND AFTER
THE TWO RF SCHEDULES (mg/kg b.wt./day)

Rat No.	Before RF	RF T = 27 h	Between two RFs	RF T = 24 h	After RF
1804	4.5	5.2 ± 0.4	6.0	7.6 ± 2.7	8.4 ± 1.7
1806	5.5	6.2 ± 0.5	5.2	7.5 ± 0.5	6.8 ± 0.8
1814	2.8	3.7 ± 0.3	5.9	7.7 ± 0.8	7.6 ± 2.6
1819	3.9	6.2 ± 1.6	7.7	6.3 ± 0.5	8.5 ± 0.1
1820	8.0	9.7 ± 1.1	11.1	11.8 ± 2.7	9.3 ± 1.4
1822	4.5	5.2 ± 0.4	6.0	5.5 ± 2.3	8.4 ± 1.7
1823	2.8	3.6 ± 0.2	15.4	7.2 ± 1.2	8.7 ± 0.4
Mean ± SE	5.2 ± 0.9	6.1 ± 0.9	7.9 ± 1.3	7.7 ± 0.8	7.8 ± 0.5

Values are means ± SE of 5 to 10 consecutive days under each condition. Those with no SE are the mean of 3 consecutive days.

of the central catecholaminergic mechanism (10,19) in both rhythms. Feeding, locomotion, and arousal level are critical functions to live for wild animals, and are known to be regulated by various neurotransmitters in many parts of the central nervous system. Therefore, it is not surprising that a structure other than the SCN can affect the rhythms of feeding behavior and activity/arousal level. Food-entrainable and MAP-induced rhythms may be controlled by multiple mechanisms in the brain, the major structures of which are in common.

In nocturnal rodents, the light-entrainable circadian oscillation plays a crucial role in the temporal organization of various physiological functions, while the SCN-independent oscillations are either masked or coupled to the light-entrainable oscillation. In humans, on the other hand, sleep-wake rhythm is driven by an intrinsic mechanism other than the oscillator driving the

rhythms of rectal temperature and melatonin production (29), and have many similar characteristics to those of MAP-induced rhythms. Both MAP-induced and human sleep-wake rhythms entrain not to the light cycle but to the zeitgebers other than the light: to the feeding cycle for the former and social cue for the latter. Circadian rhythms, which are quite unique to the human sleep-wake rhythms, are also observed in MAP-induced rhythms (17). The arousal level or alertness is a good indicator of either rhythm (19). The MAP-induced rhythm may provide a good experimental tool to investigate the multiple oscillatory system of humans as well as animals.

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