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Periodic Mother Deprivation During the Light Period Reversed the Phase of Serotonin *N*-Acetyltransferase Activity Rhythm of the Pineal Gland in Rat Pups

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SUGISHITA, M., M. TAKASHIMA, Y. TAKEUCHI, Y. KATO, T. YAMAUCHI AND K. TAKAHASHI. *Periodic mother deprivation during the light period reversed the phase of serotonin* N-*acetyltransferase activity rhythm of the pineal gland in rat pups.* PHARMACOL BIOCHEM BEHAV **46**(3) 609–615, 1993.—It has been reported that nursing mother rats can postnatally entrain the circadian rhythms of blinded rat pups, such as locomotor, drinking, and corticosterone rhythms. To gain more insight in the mechanism of the postnatal entrainment of such pups' circadian rhythms, we examined the serotonin *N*-acetyltransferase (NAT) activity rhythm in blinded rat pups subjected to periodic mother deprivation (PMD) in which mothers were periodically deprived of their pups during either half of a day. We found that only PMD during the light period shifted the phase of NAT activity rhythm in the pups. To cause a reversal of the NAT activity rhythm, it was necessary to repeat PMD for more than 6 days. PMD for 6 h each day also shifted the phase of the blinded rat pups, but it did not reverse the NAT rhythm, even when it was repeated for 10 days. In 9-h deprivation for 10 days, however, deprivation during the first 9 h of the light period reversed the phase, although the latter 9 h failed to cause reversal of the phase. On the other hand, restricted feeding of the mother took more than 11 days to reverse the phase and a foster mother in the cross-fostering experiment failed to affect the phase of pup's rhythm, when the rhythm was determined on the 11th postnatal day. These facts indicate that PMD during the light period is a potent entrainer of the pups' circadian NAT rhythms and provide a useful method of exploring the underlying mechanism of the entrainment of the pups' rhythm by the mother.

Serotonin *N*-acetyltransferase rhythm Entrainment Blinded rat pups Melatonin Circadian rhythm
Periodic mother deprivation Foster mother Restricted feeding

PRENATAL (5,6,12) and postnatal (3,7–9,13–26) maternal entrainment of the blinded pups' circadian rhythm, such as locomotor, drinking, and corticosterone rhythms, has been repeatedly investigated. It seems that there is a species or strain difference in the results of the cross-fostering study. Takahashi et al. (22) have reported that a foster mother with a rhythm reversed to that of the natural mother could entrain the adrenocortical and locomotor activity rhythms in blinded rat pups. Honma et al. (8) confirmed this finding only when the number of litter mates was as small as two but not when the number was increased to nine. On the other hand, Davis et al. (1) claimed that the foster mother could not change the phase of the rhythm of hamster pups that had been set by the natural mother. These discrepancies might be due to the weakness of a foster mother as an entrainer.

Periodic mother deprivation (PMD) is another way to entrain the pups' circadian rhythm by maternal behavioral rhythm, when the mother was deprived of the pups for either half of the day for a certain number of consecutive days. It has been demonstrated that the corticosterone rhythm of blinded rat pups was shifted when free access to the mother was allowed only during the dark period (6,18). When the prohibition of free access to the mother was restricted to the dark period, PMD did not cause any change in the phase of

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the pups' rhythm. Further, Viswanathan et al. (25) showed that PMD could entrain the pups' circadian motor activity rhythm in wild mice even after the weaning age.

Because PMD seems to be highly potent as an entrainer, it might be a useful paradigm in investigating the underlying mechanism of entrainment of the pups' rhythm by maternal factors. Shimoda et al. (18) have measured the blood corticosterone levels in the pups after weaning to determine the phase of the pups' rhythm subjected to PMD. However, it took time until the corticosterone rhythm became measurable, since it was fully developed after 4 weeks of age. Such a long period as 4 weeks makes the experiments inefficient. Further, determination of the phase on the basis of the corticosterone rhythms after weaning seems to be inaccurate, because the phase may keep shifting over the experimental period. Since the NAT rhythm is reported to appear as early as 4 days of age (4), we would be able to save time and obtain more accurate results by determination of the NAT rhythms instead of corticosterone rhythms. To obtain a rapid and accurate way to measure the pups' rhythm and to confirm that PMD is a reliable means of causing an entrainment of the pups' endogenous rhythm, in the present study we determined the NAT rhythm of blinded pups under various conditions, in particular in pups subjected to PMD.

METHOD

Wistar albino rats were obtained from Sankyo Laboratory Service. They were mated in our rat colony room after becoming acclimated to the environment for more than 2 weeks. Light conditions were automatically controlled with a 24-h cycle (light on 0800–2000 h). Temperature (24 ± 2°C) and humidity (50 ± 5%) were also controlled. Food and water were available at all times except for the experiment, where restricted feeding of the mother occurred during 2 or 4 h in the light period. Regular laboratory chow (Clea CE-2) was purchased from Clea Japan Inc.

All pups were blinded by optical enucleation under cold anesthesia within 24 h after birth (day 1). The pups were placed on ice, the skin over each eye ball was incised by a scissor, and the eye balls were removed using a forceps. We gave xylocaine locally after the operation. The pups recovered from anesthesia quickly and started to move within 15 min. To determine the 24-h patterns of NAT activity in the pineal gland, blinded pups were sacrificed by decapitation every 4 h over 24 h on the 11th postnatal day except where otherwise stated. At each sampling time five to seven pups were used; accordingly, 30–42 pups were sacrificed to determine the NAT rhythm in each group. The NAT activity was assayed by the method of Deguchi and Axerlod (2) with a minor modification.

The presence of rhythm was statistically examined by both one-way ANOVA and the least squares method (LSM). In both analyses the levels of statistical significance was 5%. When a significant difference was found by both ANOVA and LSM, we defined it as a "rhythm." The acrophase of the NAT activity rhythm was also determined by LSM. The phase shift was determined by the comparison of the acrophases of the two rhythms.

Experiment 1. Effect of PMD on the NAT Activity Rhythm in Blinded Pups

On the day of birth, all pups in each litter were divided into two groups: one was allowed free access to their own mother during the light period only (L-suckling group) and another was allowed free access to their mother during the dark period only (D-suckling group); all were reared under the same lighting conditions. Mothers were transferred between these two groups at 0800 h and 2000 h every day for 10 days. To examine the possibility that melatonin contained in milk may entrain the pups' rhythm, PMD was performed with a mother whose pineal gland and eyes were removed to eliminate the endogenous melatonin. Removal of the eye balls was done under ether anesthesia. Bleeding was terminated by pressure and xylocaine was given locally. To examine the efficacy of the operation, we determined blood levels of melatonin during the dark period in the pinealectomized, blinded mother rats using RIA developed by Kawashima et al. (10).

To determine the number of days required to reverse the phase of the rhythm, the days of PMD were shortened to six (between day 5 and 11), four (between day 7 and 11), and two (between day 9 and 11). Furthermore, to determine the minimum length of deprivation period during the light phase for the pups' rhythm to be reversed by PMD, pups were deprived of their mothers for various intervals as follows: 6 h (0800–1400 h or 1400–2000 h) or 9 h (0800–1700 h or 1100–2000 h) for 10 days.

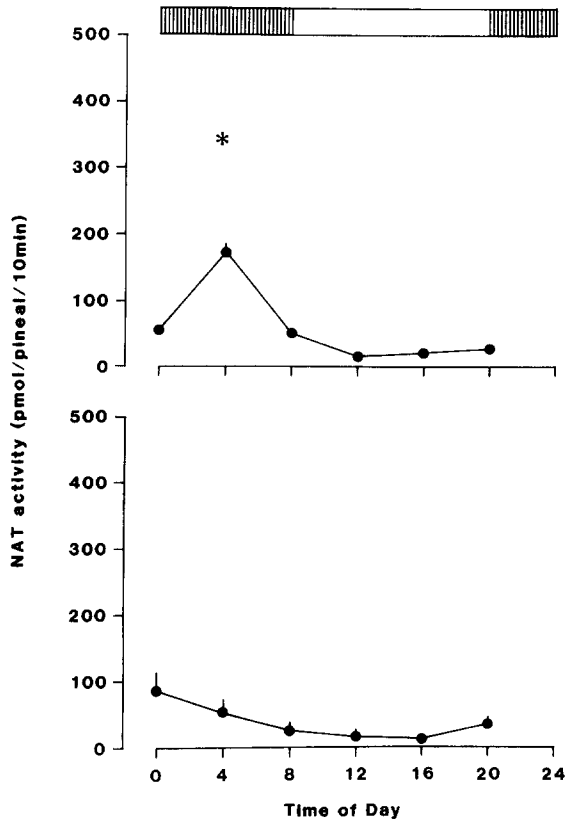

FIG. 1. Twenty-four-hour patterns of pineal NAT activity levels in two different groups of 8-day-old blinded rat pups. The abscissa shows the time of day and the ordinate the NAT activity in the pineal gland. The group in the upper part shows a statistically significant variation of the NAT activity levels, and acrophase determined by LSM is indicated by an asterisk, while the variation was not statistically significant by both one-way ANOVA and LSM. From this figure to Fig. 8, each point and bar represents the mean ± SEM of five to seven pups. From this figure to Fig. 6, the open and shaded bar at the top represents the light and dark periods during the photoperiodic cycle, respectively.

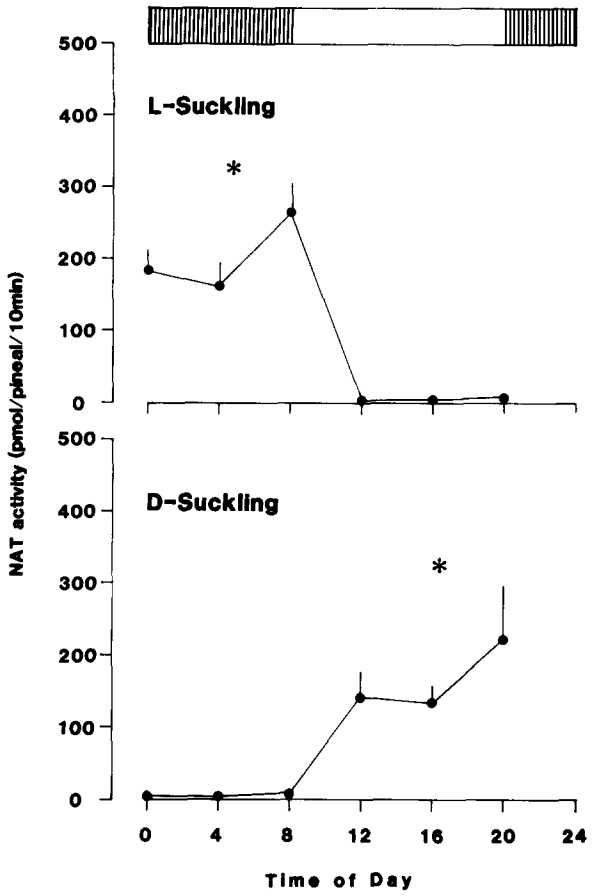

FIG. 2. Twenty-four-hour patterns of pineal NAT activity levels in 11-day-old blinded rat pups subjected to PMD. The L- and D-suckling groups are shown in the upper and lower panels, respectively. In both groups, variations of NAT activity levels were statistically significant by both ANOVA ($p < 0.01$) and LSM ($p < 0.001$). Acrophases indicated by asterisks are 0442 h in the L-suckling group and 1623 h in the D-suckling group, respectively.

Experiment 2. Effect of Cross-Fostering on the Phase of NAT Activity Rhythm

To observe the effect of a foster mother with a rhythm reversed to that of the original mother, pups who were born to an LD mother were raised by foster mothers maintained n a reversed photoperiodic cycle (DL cycle) from the day f parturition. In this experiment, the foster mothers were adapted to the reversed lighting conditions from the LD cycle (light on 0800–2000 h) to the DL cycle (light on 2000–0800 h) for several weeks before gestation and the reversal of the activity rhythm was confirmed by determination of locomotor activity using an Automex (Muroma chi Co.) (data not shown).

Experiment 3. Effect of Restricted Feeding of the Mother on the Phase of NAT Activity Rhythm

The pineal NAT activity rhythm was determined in blinded rat pups raised by mothers who were allowed free access to food and water only for 2 h (0800–1000 h) or 4 h (0800–1200 h) in a day for 11 days or 21 days from the day of birth, respectively.

RESULTS

Experiment 1. Effect of PMD on the NAT Activity Rhythm in Blinded Pups

The results obtained from the determination of 24-h patterns of NAT activity levels done at the different time using pups of 8 postnatal days were inconsistent, as shown in Fig. 1. This fact suggests that on the 8th postnatal day a clear light–dark difference in pineal NAT activity is not established yet, although 24-h patterns of pineal NAT activity showed relatively high levels during the dark period and relatively low levels during the light period. On the other hand, on the 11th postnatal day NAT activity exhibits a marked day–night difference similar to that in adult rats (Fig. 1). It is evident that the rhythm in the L-suckling group was completely in phase with the unmanipulated rats raised under the LD cycle, while that of the D-suckling group was 180 degrees out of the phase with the L-suckling group (Fig. 2). All of the four groups in the L-suckling group showed evident rhythms and their acrophases were close, varying from 0340 h to 0540 h. In the

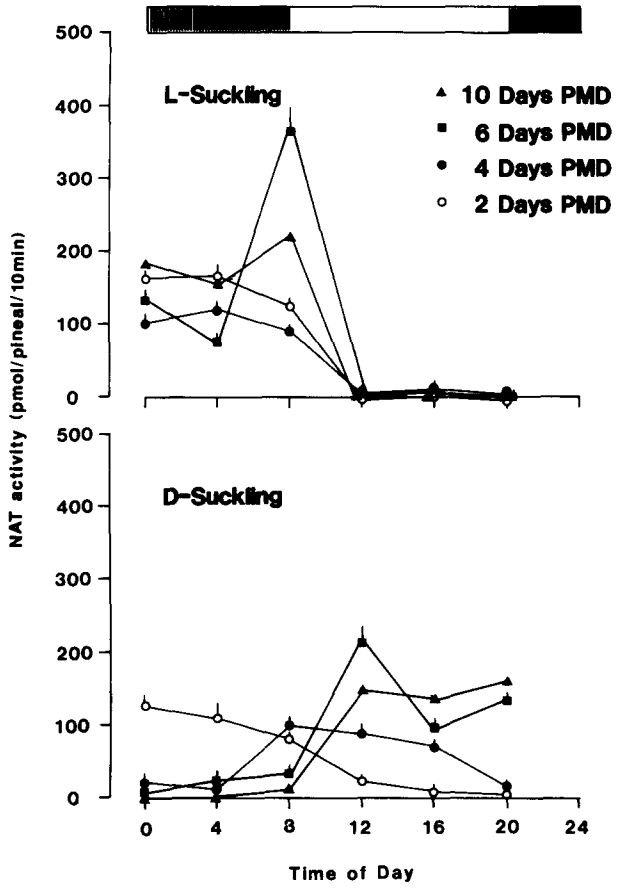

FIG. 3. Effect of change in the number of days of PMD on the shift of NAT activity rhythm in blinded rat pups. The period of PMD was shortened to 6 days (■), 4 days (●), and 2 days (○). In all eight groups it is statistically evident ($p < 0.01$ by ANOVA and $p < 0.001$ by LSM) that the NAT activity rhythms exist and acrophases are as follows: 0337 h (2-day PMD), 0348 h (4-day PMD), 0512 h (6-day PMD), and 0528 h (10-day PMD) in the L-suckling group, and 0552 h (2-day PMD), 0933 h (4-day PMD), 1540 h (6-day PMD), and 1405 h (10-day PMD) in the D-suckling group.

D-suckling groups, the acrophase was gradually delayed as the days of PMD increased. After 6 days of PMD, the rhythm was reversed, since the acrophase was approximately 12 h different from those of the L-suckling groups (Fig. 3). Two or 4 days of PMD were not sufficient to cause phase reversal of the NAT rhythm in blinded pups in the D-suckling group, because the phase shifted only 2–5 h.

Following deprivation of the pups of the mother for 9 h (Fig. 4) during the light period for 10 days, the phase of the NAT rhythm was reversed only when the deprivation was performed during the first 9 h, since the acrophase was seen at 1351 h. Nine hours of deprivation during the latter part of the light period caused a shift of only 7–9 h. Six hours of deprivation also caused a smaller phase shift compared with the 12-h deprivation group (Fig. 5). PMD during the first half of the light period seemed to exert a stronger effect, because the acrophase was 2015 h, while it was 0038 h in the group subjected to 6-h PMD during the latter half of the light period.

In the rat pups subjected to PMD for 10 days, with a mother whose endogenous melatonin was eliminated by pinealectomy and eye enucleation, the phase relationship in the

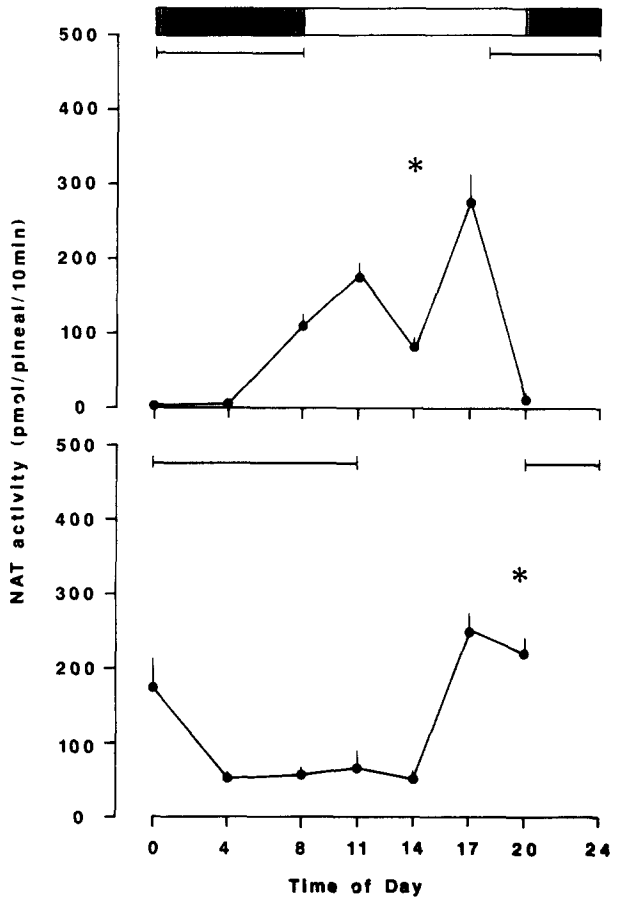

FIG. 4. Effect of deprivation of the mother for 9 h on the phase shift of the pineal NAT activity rhythm. Pups were deprived of their mothers for 9 h during the light period each day for 10 days. Pups in the upper and lower panels are those subjected to PMD during the earlier or later 9-h portions of the light period, respectively. In both groups the rhythm was evident ($p < 0.01$ by ANOVA and $p < 0.001$ by LSM), and the acrophases indicated by asterisks are 1400 h in the former and 1952 h in the latter groups, respectively.

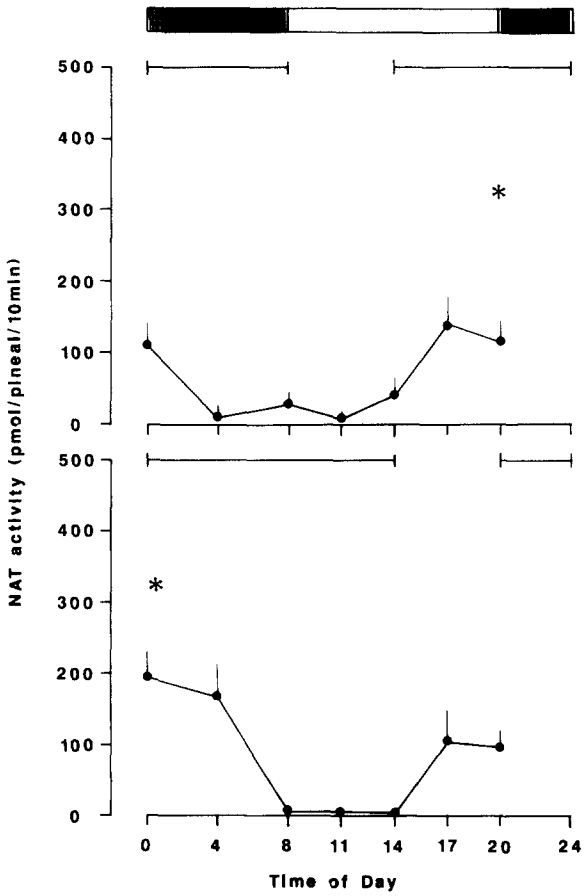

FIG. 5. Effect of deprivation of the mother for 6 h on the phase shift of the NAT activity rhythms. Pups were deprived of their mothers for 6 h during the light period each day for 10 days. Pups in the upper and lower panels are those subjected to PMD during the earlier and later 6-h periods of the light period, respectively. In both groups the rhythm was evident ($p < 0.01$ by ANOVA and $p < 0.001$ by LSM), and the acrophases indicated by asterisks are 1953 h in the former and 0015 h in the latter groups, respectively.

NAT rhythm was reversed between L- and D-suckling groups in the same way as the pups' rhythm subjected to PMD with an intact mother (Fig. 6). The acrophases were 0457 h in the L-suckling group and 1723 h in the D-suckling group. After the experiment, the plasma melatonin levels were determined during the dark period in all mother rats used in the experiments. They were lower than 25 pg/ml, which was at the daytime level, in all mothers tested.

Experiment 2. Effect of Cross-Fostering on the Phase of NAT Activity Rhythm

Twenty-four-hour patterns of NAT activity levels in the blinded rat pups, which were born to DL mothers and raised by LD mothers (DL–LD), showed the reversed phase compared with the control groups born to and raised by LD mothers (LD). The acrophases were 1652 h in the former and 0314 h in the latter group, respectively (Fig. 7). This fact indicated that foster mothers did not shift the NAT rhythm of adopted blinded pups.

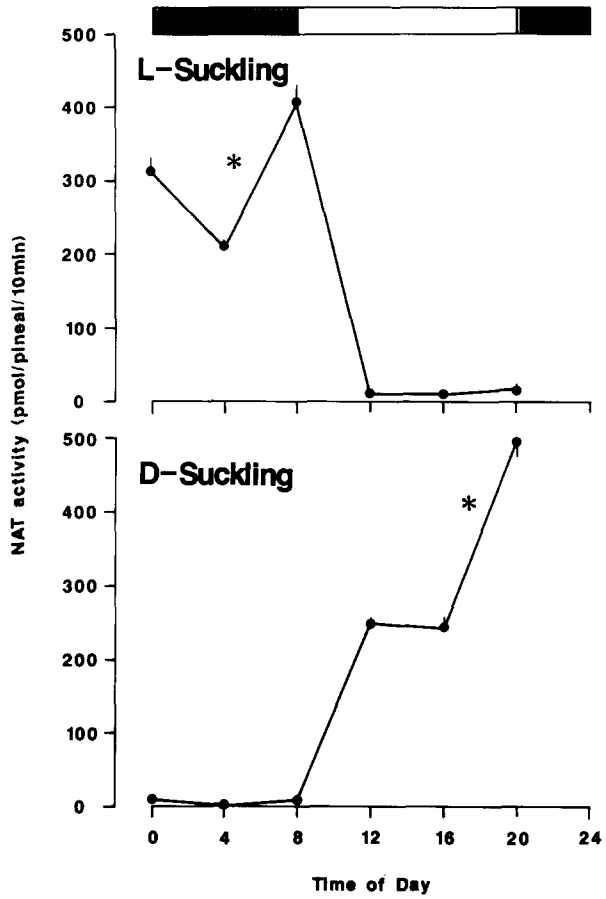

FIG. 6. Effect of reduction of endogenous melatonin by pinealectomy and optical enucleation in the nursing mother on the 24 h patterns of NAT activity rhythm in blinded rat pups subjected to PMD. The blinded pups were subjected to PMD with mothers whose eyes and pineal glands were removed on the day of parturition. In both groups the rhythm was evident ($p < 0.01$ by ANOVA and $p < 0.001$ by LSM), and the acrophases indicated by asterisks are 0430 h in the L-suckling and 1719 h in the D-suckling groups, respectively.

Experiment 3. Effect of Restricted Maternal Feeding on the Phase of the NAT Activity Rhythm in Blinded Pups

Figure 8 shows the NAT activity rhythm of blinded rat pups raised by mothers who were subjected to restricted feeding and drinking periods of 2 h (0800–1000 h) or 4 h (0800–1200 h) each day starting on postnatal day 1. On the 11th postnatal day, the NAT activity rhythm tended to have shifted to the phase of the food presentation, since the acrophase was 0915 h in the 2-h restricted feeding group and 0633 h in the 4-h restricted feeding group but was not reversed compared with the standard PMD, which showed the acrophase to be around 1500 h. In contrast, the restriction of feeding for the entire 21-day nursing period almost reversed the NAT rhythm in both groups.

DISCUSSION

The main purposes of the present study were to develop a rapid and accurate assay system of the developing endogenous rhythm in rat infants by determination of the NAT activity in the pineal gland and to demonstrate that PMD is a useful way to analyse the maternal factors influencing postnatally the pups' rhythm.

The present study confirmed and extended the previous finding that PMD shifted the phase of the blinded pups' rhythm. When free access to the mother was allowed only during the light period (L-suckling group), the phase of NAT activity rhythm did not seem to be much affected, since elevated values were observed during the dark period. On the other hand, when free access was allowed only during the dark period (D-suckling group), the rhythm was shifted 180 degrees from that of the L-suckling group. The shifted rhythm by PMD has been shown to be endogenous on the basis of the observation that corticosterone or drinking rhythm persisted in free running after weaning, and the phase relation of the free-running rhythms between L-suckling and D-suckling groups was reversed (18). Thus, the NAT rhythm shifted by PMD during the light period in the present study should be endogenous.

The reason why only D-suckling affects the phase of the rhythm remains to be clarified. However, it is most likely that such a difference might be due to the difference in the suckling phase. When the mother and pups can access mutually and

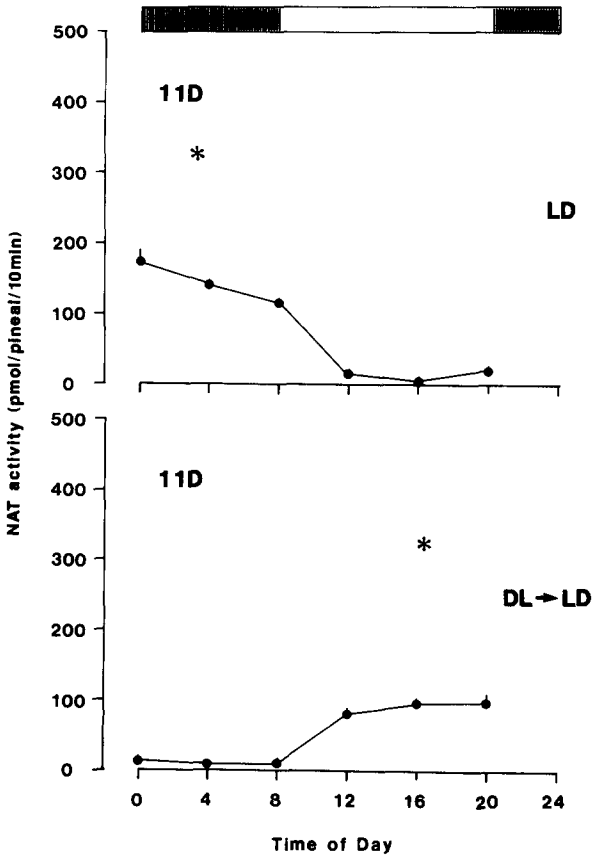

FIG. 7. Twenty-four-hour patterns of pineal NAT activity rhythm in 11-day-old blinded pups subjected to the cross-fostering experiment. Pups in the upper panel were born and raised by the mother kept under LD cycle, while pups in the lower panel were born to a DL mother and raised by a foster mother kept under the LD lighting cycle. In both groups the rhythm was evident ($p < 0.01$ by ANOVA and $p < 0.001$ by LSM), and the acrophases indicated by asterisks are 0311 h in the LD and 1620 h in the DL-LD groups, respectively.

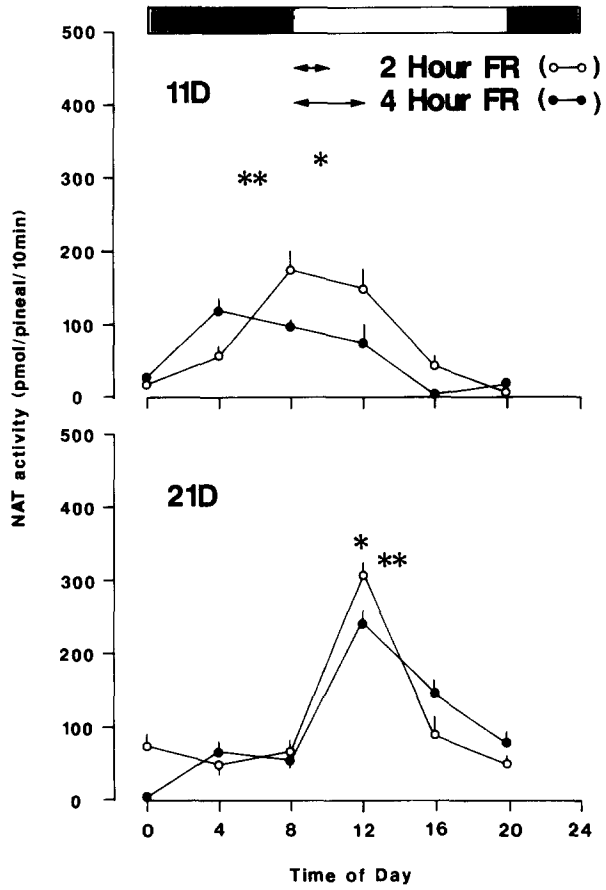

FIG. 8. Twenty-four-hour patterns of pineal NAT activity rhythm in blinded pups raised by a mother who was subjected to restricted feeding. Access of the mother to food was restricted to 0800–1000 h (○) or 0800–1200 h (●) during the light period for 11 days in the upper panel or 21 days in the lower panel. In all four groups the rhythm was evident ($p < 0.01$ by ANOVA and $p < 0.001$ by LSM), and the acrophases indicated by single asterisk for 2-h FR and double asterisks for 4-h FR are 0942 h (2-h FR) and 0532 h (4-h FR) on the 11 days and 1159 h (2-h FR) and 1311 h (4-h FR) on 21 days, respectively.

freely, pups nurse mainly during the light period (11). Accordingly, mother deprivation during the dark period did not change the pattern of suckling, while PMD during the light period unphysiologically forces pups to nurse during the dark period. Such a change in the timing of sucking milk may change the phase of the NAT rhythm. These facts suggest that either restricted suckling or stress caused by the absence of the mother can entrain the pups' circadian rhythm. The endogenous clock mechanism may be different in infants and adults in terms of susceptibility to restricted feeding or stress.

We were able to demonstrate that PMD is a more potent entrainer for the pups' circadian rhythm than restriction of the feeding time of the mother rats or a foster mother in the cross-fostering study. The present study confirmed the finding by Honma et al. (9) that restriction of feeding time of the mother influences the circadian activity rhythm of the pups. Such manipulation for 11 days shifted the phase and reversed it by 21 days. On the other hand, unexpectedly fostering by a foster mother on an alternate schedule for 11 days did not shift the phase of the NAT activity rhythm. In our previous studies, we demonstrated that a foster mother with a rhythm reversed to that of an original mother entrained the circadian rhythm of blinded rat pups during the nursing period (17,20–24). Although the difference between the present and previous reports is not readily explained, possible explanations are differences in the experimental conditions or the animal colony. The present study was done in a different institute (National Institute of Neuroscience) from the previous institute (Tokyo Metropolitan Institute for Neurosciences), and rats were obtained from a different breeder. It has been suggested that the influence of a foster mother changes depending on the experimental conditions (8).

The present study clearly demonstrated that the circadian NAT rhythm of pups could be postnatally affected by some maternal factor(s). However, although several factors are conceivable as specific ones responsible for the postnatal entrainment of the pups' rhythm, such as physical suckling of milk, a specific nutritional or hormonal substance contained in the milk, physical contact with the mother, olfactory factors, and so on, these putative factors remain to be clarified. To investigate the possibility that melatonin might be involved in the entrainment of the pups' rhythm by the mother, mother rats whose endogenous melatonin rhythm was eliminated by pinealectomy and optical enucleation were adopted in the PMD study. Pups in the D-suckling group raised by such manipulated mothers still showed phase reversal of the rhythm. This fact indicates that melatonin does not play the main role in the entrainment of the pups' pineal rhythm by the mother.

Compared with previous studies on the postnatal entrainment of the rhythm, the present paradigm may be a useful one in investigating the maternal factors affecting the phase of the blinded pups' rhythm, as previously shown by Reppert et al. (13). We showed that the number of days of PMD or the duration of deprivation of the mother significantly modifies the mode of shift of the NAT rhythm by the mother. It became evident that a minimum of 6 days of 12-h PMD is necessary to cause a reversal of the rhythm. The paradigm requiring such a short period will be convenient to analyse the maternal factors. For example, artificial feeding by intragastric tubing for 6 days will be utilized to investigate the role of specific nutritional substances, such as amino acids, carbohydrates, or fat, in the entraining mechanism. By means of this paradigm, the analysis of factors responsible for the postnatal entrainment of the pups' rhythm by the mother is in progress in our laboratory.

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