Effects of Cyclic and Continuous Total Enteral Nutrition on 24-h Rhythms of Body Temperature and Urinary Excretions

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(Received June 18, 1991)

Summary To clarify the relationship between the pattern of diet intake and circadian rhythm in man, we measured body temperature and urinary excretions at 4-h intervals over a 24-h period in 18 patients who were in vegetative states and had been receiving total enteral nutrition (TEN) for at least 4 weeks. One group of patients was given a liquid diet intraduodenally and continuously throughout a day (continuous TEN), whereas the two other groups received their daily enteral feeding during a restricted time of day, either in the daytime from 0800h to 2000h (diurnal TEN) or in the nighttime from 2000h to 0800h (nocturnal TEN). In the diurnal TEN group, there was a clear body temperature rhythm with a peak at 2000h, whose pattern was similar to the well-established body temperature rhythm in normal subjects. The nocturnal TEN group also showed a temperature rhythm, but the peak appeared at 0400h. The continuous TEN group did not show any consistent body temperature rhythms. These effects of the schedule of TEN were quite similar to those on the circadian cortisol rhythm reported previously (J. Nutr. Sci. Vitaminol., 35, 639–647, 1989). In contrast to the body temperature rhythm, the rhythm of urinary excretions of water, sodium and potassium was little influenced by the schedule of TEN, showing a normal pattern with more excretions during the daytime in every group. Essentially the same effects were confirmed in a patient who received the three schedules of TEN in rotation for 5 weeks of each schedule. In conclusion, the timing of diet intake remarkably modifies the 24-h rhythms of body temperature and adrenocortical activity in man, as in laboratory animals, while it has no effect on the urinary excretion rhythm.

Key Words twenty-four-hour rhythm, body temperature, total enteral nutrition, diet intake, urinary excretion
During the past decade the role of timing of food presentation as a zeitgeber of circadian rhythms has been proposed in laboratory animals. This is based largely on the observations in rats and squirrel monkeys that restricted daily feeding schedules synchronize many behavioral and physiological activities, such as locomotor activity, food lever-pressing, glucocorticoids secretion, body temperature and intestinal enzyme activity (for a review, see 1). In human subjects, however, scant information is available about such a synchronizing role of food intake.

We have examined the circadian pattern of plasma cortisol in patients who had been kept under various schedules of total enteral nutrition (TEN). Our previous results (2, 3) clearly showed that the phase of the cortisol rhythm was shifted by changing the daily pattern of diet infusion, suggesting a synchronizing effect of food intake on the adrenocortical rhythm in man as well as in laboratory animals. To extend this view and to confirm the relationship between diet intake and circadian rhythm of other physiological activities in man, in this study we examined 24-h patterns of body temperature and urinary excretions in the same patients as in the previous study (3): that is, they were kept under a schedule of either continuous or cyclic TEN.

METHODS

Subjects. The subjects of this study were 4 male and 14 female hospitalized patients (57–86 years old) having either cerebral infarction or traumatic intracranial hematoma. Although all patients were in vegetative states because of severely disturbed consciousness (Glasgow coma scale of 3–5), they were good in general conditions, and free of any specific diseases, such as infective diseases, renal dysfunction, hypertension or endocrine and metabolic diseases. The details of their clinical profiles were described previously (3). None had received medications interfering with urinary excretion and body temperature at the time of the study. Informed consent for the circadian study was obtained from the family of each patient. The procedure was in accord with the ethical standards of the Committee on Human Experimentation of this university.

Schedules of total enteral nutrition. Nutritional support of the patients was achieved by total enteral nutrition (TEN): that is, they were given a chemically defined diet (Elental, Morishita Pharm., Osaka) as the only source of nutrition through a chronically inserted nasoduodenal tube. The composition of the diet was 79.4% dextrin, 17.6% amino acids, 0.6% soy bean oil, 2% minerals and 0.4% vitamins on a weight basis. The diet was dissolved in water at the concentration of 0.21–0.27 g/ml (0.8–1.0 kcal/ml). The patients were randomly divided into 3 groups of 6 patients each. In one group, the diet was infused continuously at the rate of 50–63 ml/h to give 1,200–1,500 kcal a day (continuous TEN). In the two other groups the diet was infused only during a restricted time of day, either in the daytime from 0800 h to 2000 h (diurnal TEN) or in the nighttime from 2000 h to 0800 h (nocturnal TEN). It was given every day at the rate of 100–125 ml/h to give
the same amount of the diet per day as that in continuous TEN. Each patient was kept under either type of infusion schedule for at least 4 weeks before the measurement of body temperature and urinary excretions. In addition, there was a female patient (74 years old) who was first kept under diurnal TEN for 5 weeks, then under continuous TEN for 5 weeks, and finally under nocturnal TEN for 5 weeks.

Illumination was provided by natural light and also by fluorescent strip lights usually turned on at 0700 h and off at 2100 h. Room temperature was kept at 18–28°C.

Sample collection and assays. After at least 4 weeks on the steady infusion of the diet, body temperature was measured at 4-h intervals over a 24-h period by placing an ordinary clinical mercury-in-glass thermometer in the axilla. Then, urine samples were collected from a chronically inserted Foley catheter. After measuring urine volume in the 4-h period, an aliquot was picked up and stored at −80°C until assays. Urinary concentrations of sodium and potassium were determined by the method of ion-specific electrode (NOVA 1 sodium/potassium analyzer, NOVA Biochemical Co., USA). In the patient who had serially received 3 schedules of TEN, body temperature and urinary excretions were measured at 4-h intervals every day over a 7-day period at the end of each infusion schedule.

Data analysis. Values were expressed as mean ± SE. Data were analyzed first by analysis of variance (ANOVA) to examine whether there was any significant effect of clock time. Then, the cosinor method (4) was used for detection and quantitative characterization of 24-h rhythms. In brief, a cosine curve with a period of 24 h was fitted to the data using the method of least squares, and the following three main parameters were estimated: mesor (24-h rhythm-adjusted mean), acrophase (peak time) and amplitude. The differences of the parameters between the groups were tested by Student’s t-test.

RESULTS

Figure 1 shows the 24-h patterns of axillary temperature under continuous and cyclic TEN. In the diurnal TEN group, body temperature was low at night and early morning and high in the afternoon/early evening. ANOVA revealed that the effect of clock-time on body temperature was highly significant ($p < 0.005$). In contrast, body temperature of the nocturnal TEN group rose at night and fell in the daytime. This change was also significant with respect to clock-time ($p < 0.01$). In the continuous TEN group, however, body temperature did not show any significant change with clock-time.

In order to clarify the temporal characteristics of body temperature in the three groups, the cosinor method was applied to the data. As summarized in Table 1, there was a significant 24-h rhythm in both groups of diurnal and nocturnal TEN, whereas no rhythm was detected in the continuous TEN group. The average temperature (mesor) was almost the same in the three groups. The clock-time
Fig. 1. Rhythms of body temperature in the diurnal (left), continuous (center) and nocturnal (right) TEN groups. Shaded bars and black bars indicate the times of diet infusion and lights-off, respectively. \( p \) values are those from ANOVA.

Table 1. Cosinor analysis of the rhythms shown in Figs. 1, 2 and 3.

|                        | Mesor (°C)       | Acrophase (h)    | % amplitude |
|------------------------|------------------|------------------|-------------|
| Body temperature       |                  |                  |             |
| Diurnal TEN            | 36.8±0.09        | 1922±0043        | 1.12±0.21***|
| Continuous TEN         | (36.6±0.08)      | (0326±0209)      | (0.39±0.22)**|
| Nocturnal TEN          | 36.8±0.06        | 0246±0042        | 0.97±0.18** |
| Urine volume (ml/4h)   |                  |                  |             |
| Diurnal TEN            | 192±19           | 1230±0059        | 53.4±13.8*  |
| Continuous TEN         | 193±14           | 1644±0050        | 45.3±9.5**  |
| Nocturnal TEN          | 177±24           | 1608±0112        | 50.0±11.7** |
| Urinary Na (mEq/4h)    |                  |                  |             |
| Diurnal TEN            | 5.15±1.00        | 1112±0102        | 95.5±21.0** |
| Continuous TEN         | 8.72±0.88        | 1454±0053        | 64.3±13.1** |
| Nocturnal TEN          | 6.99±0.81        | 1449±0038        | 100.5±16.5**|
| Urinary K (mEq/4h)     |                  |                  |             |
| Diurnal TEN            | 3.09±0.38        | 1123±0052        | 73.3±16.0** |
| Continuous TEN         | 5.22±0.73        | 1310±0101        | 48.9±13.1*  |
| Nocturnal TEN          | 4.78±0.45        | 1431±0110        | 54.1±12.3** |

\* \( p < 0.05 \); \** \( p < 0.01 \); ns, not significant.

when a peak value appeared (acrophase) in the diurnal TEN group was 1922 h, which was different by about 7.5 h from that in the nocturnal TEN group (0246 h), whereas there was no significant difference in the amplitude of the rhythm between the two groups. Infusion pattern of nutrients thus modified the body temperature rhythm, shifting its phase without noticeable effects on its amplitude and the average level.

Rhythms of urine volume in the three groups are shown in Fig. 2. There was
a significant effect of clock-time in every group. An analysis by the cosinor method revealed that the mesor and the %-amplitude were almost the same in the three groups (Table 1). The acrophase of the diurnal TEN group (1230 h) seemed slightly different from those of the continuous (1644 h) and nocturnal (1608 h) TEN groups, but these differences were statistically not significant.

Urinary excretions of sodium and potassium also showed 24-h rhythms in all groups (Fig. 3 and Table 1). Although there was a slight difference in the mesor and the %-amplitude between the groups, the acrophase was almost the same in the three groups, appearing between 1112 h and 1454 h. Thus, in contrast with the temperature rhythm, the urinary excretion rhythm was little influenced by infusion...
Fig. 4. Rhythms of body temperature in a patient under diurnal (top), continuous (middle) and nocturnal (bottom) TEN. The shaded bars indicate the times of diet infusion.

Table 2. Cosinor analysis of the rhythms shown in Figs. 4 and 5.

|                          | Mesor     | Acrophase (h) | % amplitude |
|--------------------------|-----------|---------------|-------------|
| Body temperature (°C)    |           |               |             |
| Diurnal TEN              | 36.5±0.06 | 1618±0038     | 1.31±0.19** |
| Continuous TEN           | (35.7±0.87) | (2351±0243)   | (0.27±0.12)** |
| Nocturnal TEN            | 36.5±0.05 | 0206±0055     | 0.85±0.17** |
| Urine volume (ml/4h)     |           |               |             |
| Diurnal TEN              | 291±33    | 1203±0057     | 57.0±13.5** |
| Continuous TEN           | 289±30    | 1115±0114     | 47.8±14.7*  |
| Nocturnal TEN            | 366±21    | 1312±0040     | 40.4±7.9**  |

*p<0.05; **p<0.01; ns, not significant.

To confirm further the effects of infusion pattern on the rhythms, next, axillary temperature and urine volume were measured at 4-h intervals throughout a consecutive 7-day period in one patient. When the patient was kept under diurnal TEN for 5 weeks, her temperature showed a consistent 24-h rhythm with an acrophase of 1618 h, whereas no consistent rhythm was detected when the same patient was kept under the continuous TEN for 5 weeks (Fig. 4 and Table 2). A significant 24-h rhythm appeared again when the patient was kept under the nocturnal TEN for 5 weeks, with an acrophase of 0206 h which was different from that found under diurnal TEN. In contrast, urine volume showed a quite similar 24-h rhythm under the three schedules of TEN, with an acrophase of 1115–1312 h and a %-amplitude of 40.4–57.0 (Fig. 5 and Table 2).

J. Nutr. Sci. Vitaminol.
DISCUSSION

In the previous study with the same patients as in this study (3), we demonstrated that the circadian pattern of plasma cortisol level, particularly its phase, was substantially modified by the schedule of TEN, suggesting a synchronizing role of diet intake for the cortisol rhythm. A quite similar effect of TEN was found in the present study on the 24-h pattern of body temperature: that is, in patients with diurnal TEN, axillary temperature showed clear 24-h fluctuations with a peak at 2000 h, whose pattern was similar to the well-established temperature rhythm in normal subjects. This is not a surprising result because the schedule of diurnal TEN can be considered as a mimicry of diurnal feeding habits of normal man. The temperature rhythm was, however, delayed by some 8 h in nocturnal TEN to have a peak at 0400 h. The cosinor analysis also revealed an about 7.5-h shift of the acrophase without noticeable change in the amplitude in nocturnal TEN. Thus, the phase of the temperature rhythm shifts on changing the time of diet infusion.

It has been established in normal human subjects that the temperature rhythm is generated by an endogenous mechanism and persists even under total starvation and also independently of the cycle of rest-activity or sleep-wakefulness (5). Thus the present results may suggest a possible role of diet as a synchronizer of the endogenous mechanism controlling the temperature rhythm. However, it should be noted that the present subjects were unconscious and in vegetative states for more than 4 weeks. It is therefore also possible that the endogenous mechanism itself and/or synchronizing mechanism may be, more or less, impaired. On the other hand, food intake is recognized as having a specific dynamic action, leading to an
increase in metabolism and heat production, which in turn can lead to an increase in body temperature. Since body temperature is elevated at the phase when diet infusion occurs, it seems possible that the thermodynamic action of diet intake may play a role in the rhythmic fluctuation of body temperature. In other words, the temperature rhythm observed in the present study may be not endogenous but simply a passive response to diet intake. Further studies are needed to discriminate these two possible mechanisms.

In contrast to the temperature rhythm, the 24-h pattern of urinary excretions of water, sodium and potassium was little influenced by the schedule of TEN to show a rather consistent rhythm with more excretions during the daytime, which was similar to the well-known rhythm in normal subjects (5). Muratani et al. (6) reported that there was no significant difference in the circadian urinary rhythms between patients receiving continuous total parenteral (intravenous) nutrition and those on an ordinary hospital diet. In addition, there are several reports that the urinary potassium excretion rhythm is hardly modified by the pattern of food and water intake both in man and laboratory animals (7–9). Our results are in good agreement with these previous observations, and indicate that the urinary excretion rhythm is synchronized by some factor(s) other than food and water intake. It is rather surprising that the urinary excretion rhythm was kept almost normal though the present subjects were unconscious. This implies the existence of some powerful environmental factor(s) that can synchronize the rhythm effectively.

Thus, the present study, together with our previous results, indicates that the pattern of diet intake substantially modifies the temperature rhythm as well as the adrenocortical rhythm, while it has no effect on the urinary excretion rhythm. It is evident, therefore, that the phase relationship between rhythms can be kept normal only when feeding (diet infusion) pattern is diurnal, but is disturbed under a nocturnal or continuous feeding pattern. Similar splitting of rhythms has been demonstrated in laboratory animals kept under constant light and also in human subjects living in isolation without time cues (5,10). Although there is, at present, little information about effects of such rhythm disturbance on body functions, our present findings may provide a clue to solve some problems in clinical nutrition and medicine. For example, it has been recognized that an abnormal circadian pattern of food intake, night-eating habit, is one of the contributing factors for some metabolic and endocrine disorders, such as obesity, glucose intolerance and hypercholesterolemia (11). There are also reports that in parenteral nutrition continuous feeding is nutritionally less beneficial than cyclic feeding (12,13). Undoubtedly, these effects of feeding pattern are intimately associated with those of the circadian rhythms.

This study was partly supported by Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture of Japan.
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