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# The Parathyroid Hormone Circadian Rhythm Is Truly Endogenous—A General Clinical Research Center Study*

GHADA EL-HAJJ FULEIHAN, ELIZABETH B. KLERMAN, EMERY N. BROWN, YONG CHOE, EDWARD M. BROWN, AND CHARLES A. CZEISLER

*Endocrine-Hypertension Division, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School (G.E.-H.F., E.B.K., E.M.B., C.A.C.); and the Statistics Research Laboratory, Department of Anesthesia, Massachusetts General Hospital, Harvard Medical School (E.N.B., Y.C.), Boston Massachusetts 02115*

**ABSTRACT**

While circulating levels of PTH follow a diurnal pattern, it has been unclear whether these changes are truly endogenous or are dictated by external factors that themselves follow a diurnal pattern, such as sleep-wake cycles, light-dark cycles, meals, or posture.

We evaluated the diurnal rhythm of PTH in 11 normal healthy male volunteers in our Intensive Physiologic Monitoring Unit. The first 36 h spent under baseline conditions were followed by 28–40 h of constant routine conditions (CR; enforced wakefulness in the strict semirecumbent position, with the consumption of hourly snacks). During baseline conditions, PTH levels followed a bimodal diurnal rhythm with an average amplitude of 4.2 pg/mL. A primary peak ($t_{1max}$) occurred at 0314 h, and the secondary peak ($t_{2max}$) occurred at 1726 h, whereas the primary and secondary nadirs ($t_{1min}$ and $t_{2min}$) took place, on the average, at 1041 and 2103 h, respectively. This rhythm was preserved under CR conditions, albeit with different characteristics, thus confirming its endogenous nature. The serum ionized calcium ($Ca_i$) demonstrated a rhythm in 3 of the 5 subjects studied that varied widely between individuals and did not have any apparent relation to PTH. Urinary calcium/creatinine (UCa/Cr), phosphate/Cr ($UPO_4$/Cr), and sodium/Cr (UNa/Cr) ratios all followed a diurnal rhythm during the baseline day. These rhythms persisted during the CR, although with different characteristics for the first two parameters, whereas that of UNa/Cr was unchanged. In general, the temporal pattern for the UCa/Cr curve was a mirror image of the PTH curve, whereas the $UPO_4$/Cr pattern moved in parallel with the PTH curve.

In conclusion, PTH levels exhibit a diurnal rhythm that persists during a CR, thereby confirming that a large component of this rhythm is an endogenous circadian rhythm. The clinical relevance of this rhythm is reflected in the associated rhythms of biological markers of PTH effect at the kidney, namely UCa/Cr and $UPO_4$/Cr. (*J Clin Endocrinol Metab* **82:** 281–286, 1997)

DIURNAL VARIATIONS in PTH levels were demonstrated as early as the 1960s (1–3) and were confirmed in recent studies using the intact PTH assay, with peak levels occurring in the early morning (4–9). It is possible that the episodic endogenous secretion of PTH, such as that associated with diurnal changes, may have an important effect on bone remodeling. Whereas an increasing body of evidence demonstrates early morning increments in several markers of bone resorption (10, 11), Ledger *et al.* (12) recently showed that PTH was not the mediator of this diurnal pattern of bone resorption. It has, however, been suggested that biological fluctuations in circulating levels of PTH may have an anabolic effect on bone. Indeed, several studies have documented a diurnal rhythm for markers of bone formation such as osteocalcin and the propeptide of type I collagen (10, 13, 14), both of which peaked in the early morning hours and, in the case of osteocalcin, coincided with the maximal level of PTH (15). In addition, two recent studies documented a greater amplitude for the diurnal rhythm of intact PTH levels in men than in women (6) and in normal than in osteoporotic subjects (8).

Serum calcium, the major modulator of PTH secretion, follows a diurnal rhythm (5, 7, 8, 16–19), yet its impact on the circadian pattern of PTH is controversial, (2, 5–8). Equally debatable is the effect of sleep on the PTH rhythm. A study using cross-spectral analysis suggested that the nocturnal rise in PTH levels was related to sleep stages 3 and 4 (3), whereas more recently, it was demonstrated that shifts in the timing of sleep did not alter the timing of the PTH nocturnal peak in six healthy individuals (20). The same group also demonstrated that a 96-h fast completely abolished the nocturnal rise in PTH that is present under normal conditions (9). Therefore, it has remained unclear whether the consistently observed nocturnal rise in PTH is truly endogenous and independent of nocturnal events such as sleep, posture, and hemodilution or whether it is secondary to the diurnal changes in these parameters.

In this study, we applied a constant routine (CR) protocol, a technique widely used in our laboratory, in which posture, wake status, and meal consumption are maintained in near-constant conditions, to test the hypothesis that the PTH diurnal rhythm has an endogenous circadian component (21). To assess the clinical significance of the presumptive circa-

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Address all correspondence and requests for reprints to: Ghada El-Hajj Fuleihan, M.D., Endocrine-Hypertension Division, Brigham and Women's Hospital, Harvard Medical School, 221 Longwood Avenue, Boston, Massachusetts 02115.

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dian nature of PTH diurnal rhythm, parameters known to reflect PTH action at the kidney, namely urinary calcium and phosphate excretion, were also measured. Serum ionized calcium ($Ca_i$) concentration was measured in the last five subjects studied.

## Subjects and Methods

### *Subjects*

We studied 11 healthy men (mean age ±SD, 22.6 ± 2.4 yr) recruited through advertisements distributed on local campuses. They were all documented to be normal through screening with a medical history, physical examination, and laboratory studies. To avoid any confounding effects of obesity on the PTH-vitamin D axis (22), only subjects within the range of 85–115% of ideal body weight, as determined from the Metropolitan Life Tables, were selected for study. No prescriptions, over the counter medications, caffeine, or cigarettes were allowed for 1 week before study entry. Subjects were free of medication and other drug use as verified by complete toxicologic screening of blood and urine before the study. They reported no history of travel across more than one time zone for 3 months before study entry. The study was reviewed and approved by the committee for the protection of human subjects at Brigham and Women's Hospital. Informed consent was obtained from each subject before participation.

### *Study protocol*

All subjects were studied in the Intensive Physiologic Monitoring Unit of the General Clinical Research Center at the Brigham and Women's Hospital. On the first day of admission, each subject had a catheter inserted into a forearm vein for blood drawing and a rectal temperature sensor placed for recording of core body temperature. Urine was collected every 3–5 h while the subjects were awake. Each subject was scheduled to sleep for 8 h at his habitual bedtime, as determined by averaging the last 7 days of self-reported sleep log data. The subjects were studied in an environment free of time cues. They spent 36 h under baseline conditions, which included two 8-h sleep episodes, the second of which was immediately followed by 28–40 h of CR. Wake time was at the same clock hour for baseline day and CR. When subjects were awake, lighting was maintained at approximately 150 lux. During the baseline day, subjects were ambulatory and encouraged to maintain their usual daily activities. They were fed an isocaloric diet (consisting of 50% carbohydrates, 30% fat, and the remainder protein) that they ate in three meals and a snack served at approximately 0800, 1200, 1700, and 2000 h, respectively. The CR procedure consisted of restricting subjects to semirecumbent wakefulness, which was maintained by trained technicians who remained with the subject throughout the CR. Each subject received identical hourly snacks consisting of solid food, which over 24 h matched the nutritional supplementation provided to them during the baseline day. The total caloric intakes during the baseline day and the CR were 2687 ± 169 (mean ± SD) and 2529 ± 315 cal, respectively. The total calcium, phosphorus, and magnesium intakes were 1060 ± 255, 1711 ± 371, and 346 ± 42 mg on the baseline day and 540 ± 462, 1476 ± 296, and 370 ± 73 mg during the CR, respectively. Sodium and potassium intakes during the baseline day were 3554 ± 449 and 4177 ± 421 mg for the baseline day and 2882 ± 517 and 3824 ± 524 mg for the CR day, respectively.

### *Blood and urine sampling*

Throughout the protocol, blood was drawn every 20 min for measurement of plasma PTH and cortisol levels. Serum $Ca_i$ levels were measured hourly for the last five subjects who participated in the study. A specially designed and manufactured 18-gauge iv placement unit with side port holes (Deseret Pharmaceutical Co., Sandy, UT) was used to facilitate the collection of blood without disturbing the subjects, even during sleep. Urine collection was scheduled every 3–5 h during wake time on the baseline day and throughout the CR. Urine volume was measured, and an aliquot was saved for assay of urinary sodium (UNa), calcium (UCa), phosphate ($UPO_4$), and creatinine (UCr).

### *Laboratory tests*

Blood for $Ca_i$ determination was collected anaerobically and measured with a Nova 7 calcium analyzer (Nova Biomedical, Waltham, MA), which has a precision of 0.59% (normal range, 4.48–5.38 mg/dL). UNa, UCa, $UPO_4$, and UCr were determined by a reference clinical chemistry laboratory (Bioran Laboratories, Cambridge, MA).

Plasma intact PTH was measured by the Allegro immunoradiometric assay (Nichols Institute, San Juan Capistrano, CA). The detection limit of the assay is 1 pg/mL (normal range, 10–65 pg/mL), and the intra- and interassay coefficients of variation are 2% and 10%, respectively.

Plasma cortisol was measured by a RIA (Baxter Dade Diagnostic, Cambridge, MA). The detection limit of the assay is 1 $\mu$g/dL (normal ranges: 0800 h, 9–24 $\mu$g/dL; 1600 h, 3–12 $\mu$g/dL); and the intra- and interassay coefficients of variation are 4.4% and 7.3%, respectively.

### *Statistical analysis*

To pool data across subjects at the same circadian phase and to conduct analyses on the same time scale, we referenced all data to each subject's wake time. The average wake time across subjects was 0802 h. For both the baseline day and the CR, circadian rhythm parameters were estimated from a two-harmonic regression model (23) that was applied to each individual's calcium, cortisol, PTH, and core temperature data. For each data set the analysis yielded estimates of the phase of the rhythm minimum ($t_{min}$), the phase of the rhythm maximum ($t_{max}$), and its amplitude. The amplitude estimates were computed as half the difference between the maximum and the minimum of the fitted curve (23). For bimodal rhythms (*i.e.* those with more than one maximum and minimum), we denote the primary and secondary peaks as $t_{1max}$ and $t_{2max}$, respectively, and the primary and secondary nadir as $t_{1min}$ and $t_{2min}$. Population estimates of the rhythm maximum, minimum, and amplitude were calculated for PTH, cortisol, and temperature from estimates of their respective population rhythm curves. The population rhythm curve for each variable was estimated by averaging the coefficients from each individual subject's two-harmonic regression fit. The error curves about each population rhythm estimate were constructed by calculating the pointwise 95% confidence intervals. For PTH, population estimates of phase and amplitude were also computed as the mean and median of the individual phase and amplitude estimates. The median is a more representative summary because the sample is small and not clearly Gaussian.

The population rhythms of urinary electrolytes were estimated by harmonic regression methods from pooled data for individual subject's urinary electrolyte data normalized by UCr. The number of harmonics included in the model for each urinary variable was the smallest number whose highest coefficients were statistically significant. The error curves for the urinary electrolyte population rhythm estimates were constructed as described above.

To assess the relationship between serum PTH and UCa and between serum PTH and $UPO_4$ during the baseline day and the CR, we computed the correlation between the estimated population diurnal rhythms for PTH and UCa/Cr and for PTH and $UPO_4$/Cr at 0.5-h lags between 0–24 h. The maximum positive and negative correlations between the above variables with their corresponding lag times were calculated.

## Results

Plasma cortisol and core body temperature show the expected circadian rhythm for both variables on the baseline day and the CR (Fig. 1 and Table 1). All fits of the two-harmonic regression model to data from individual subjects were statistically significant on both the baseline day and the CR.

An examination of the temporal profile for PTH in Fig. 1 and Table 1 reveals a bimodal diurnal rhythm under baseline conditions with a primary amplitude of 4.25 ± 0.19 pg/mL (n = 10 subjects). The PTH rhythm was uniphasic under CR conditions; however, although the nadir was unchanged, the maximum occurred earlier, and the amplitude was slightly blunted (2.10 ± 0.11 pg/mL; n = 11 subjects). All model fits

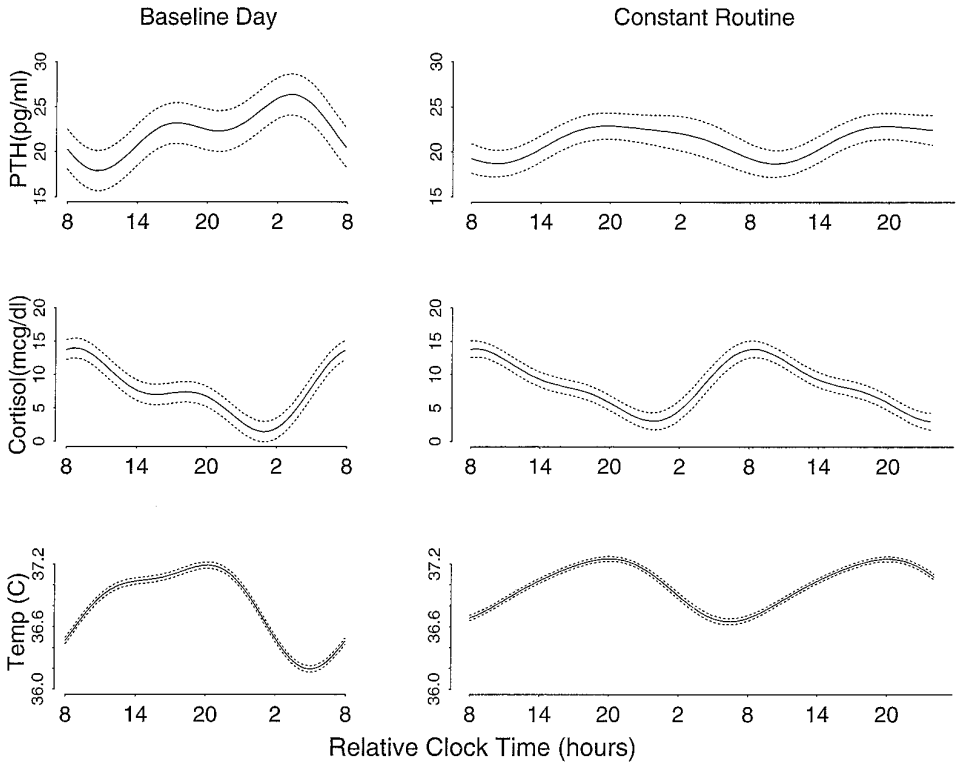


FIG. 1. Estimated population mean rhythm curves (±2 SD) for plasma PTH, cortisol, and core body temperature (Celsius) on the baseline day and during the CR. The population mean rhythm curve for each variable was estimated by averaging the coefficients from each individual subject's two-harmonic regression fit. The error curves were constructed by computing pointwise 95% confidence intervals based on the population regression parameter estimates.

**TABLE 1.** Times of the maxima and minima and amplitudes of the average curves for PTH, cortisol, and core temperature

| Marker | Baseline day | | | | | Constant routine | | |
|---|---|---|---|---|---|---|---|---|
| | $t_{1\ max}$ | $t_{2\ max}$ | $t_{1\ min}$ | $t_{2\ min}$ | Amp | $t_{1\ max}$ | $t_{1\ min}$ | Amp |
| PTH (pg/mL) | 0314 | 1726 | 1041 | 2103 | 4.25 | 2000 | 1008 | 2.10 |
| Cortisol (μg/dL) | 0843 | 1816 | 0058 | 1543 | 6.27 | 0824 | 2347 | 5.40 |
| CT | 2011 | | 0459 | | 0.50 | 2030 | 625 | 0.30 |

All times are reported in relative clock time (hours) referenced from an average wake time of 0802 h. Amplitudes are reported in units of concentration.

of PTH were statistically significant. The phase and amplitude estimates determined from the population rhythm estimates of PTH were most similar to the median of the individual phase and amplitude estimates (Table 2).

Serum $Ca_i$ displayed a significant circadian rhythm in three of five subjects (subjects 1306V, 1310V, and 1315V) during the baseline day and in three of five subjects (subjects 1273V, 1306V, and 1310V) during the CR (Table 3). However, the phase estimates were highly variable between individuals and were not related to the corresponding PTH phase estimates within individuals in any consistent manner (Tables 2 and 3).

Urinary Ca/Cr displayed a bimodal circadian rhythm, with an amplitude of 0.02 pg/mL (Fig. 2 and Table 4). The nocturnal decrease in urinary calcium excretion persisted during the CR, but the pattern became unimodal, with a larger amplitude of 0.03 (Fig. 2 and Table 4). Urinary $PO_4$/Cr also followed a bimodal diurnal rhythm, with an amplitude of 0.25, that became unimodal during the CR, with a reduced amplitude of 0.12 (Table 4 and Fig. 2). Urinary Na/Cr displayed a robust unimodal rhythm that was essentially unchanged during the CR (Fig. 2 and Table 4).

On the baseline day, the maximum positive (negative) correlation between UCa/Cr and PTH was 0.57 (−0.94) at a lag of 6.5 h (−0.5 h). During the CR, the maximum positive (negative) correlation between UCa/Cr and PTH was 0.86 (−0.87) at a lag of 13.5 h (2.5 h). On the baseline day, the maximum positive (negative) correlation between $UPO_4$/Cr and PTH was 0.50 (−0.97) at a lag of 0 h (16 h). During the CR, the maximum positive (negative) correlation between $UPO_4$/Cr and PTH was 0.80 (−0.54) at a lag of −2.5 h (9.5 h). In general, the UCa/Cr curve was the inverse of the estimated PTH population rhythm, whereas the $UPO_4$/Cr rhythm moved in parallel with the rhythm of PTH.

## Discussion

Our study confirms the diurnal nature of PTH levels, with a major peak occurring at approximately 0100–0300 h, a trough occurring at approximately 1000–1100 h, and an average amplitude of 4–5 pg/mL. As all model fits of PTH data were statistically significant under CR conditions, the PTH rhythm has an endogenous component that is not the result of environmental conditions such as diet, posture, or sleep-wake-related events. To our knowledge, this is the first study

**TABLE 2.** Times of the maxima and minima and amplitudes of the individual fitted curves for plasma PTH levels

| Subject | Baseline day | | | | | Constant routine | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | $t_{1\ max}$ | $t_{2\ max}$ | $t_{1\ min}$ | $t_{2\ min}$ | Amp | $t_{1\ max}$ | $t_{2\ max}$ | $t_{1\ min}$ | $t_{2\ min}$ | Amp |
| 1131V | 0442 | 1829 | 1144 | 2312 | 4.33 | 2319 | | 0916 | | 2.87 |
| 1132V | 2200 | | 0822 | | 4.85 | 2250 | 0854 | 1234 | 0549 | 2.17 |
| 1152V | 0445 | 1743 | 1115 | 2312 | 2.94 | 1736 | 0439 | 0946 | 0241 | 2.36 |
| 1154V | 1453 | 0011 | 0715 | 2025 | 3.24 | 1629 | | 0816 | | 2.42 |
| 1216V | 0427 | 1716 | 1135 | 2145 | 10.60 | 1818 | 0353 | 1102 | 2320 | 5.78 |
| 1265V | | | | | | 0605 | | 1509 | | 2.36 |
| 1273V | 0150 | 1625 | 0927 | 1937 | 3.44 | 1945 | | 0910 | | 1.93 |
| 1306V | 0314 | 1650 | 1029 | 2055 | 5.52 | 1959 | | 1107 | | 2.68 |
| 1310V | 2235 | | 1407 | | 2.55 | 0324 | | 1215 | | 2.58 |
| 1315V | 0432 | 1928 | 1233 | 2045 | 7.06 | 2140 | | 0634 | | 2.53 |
| 1344V | | | | | | 1810 | | 0932 | | 3.00 |
| Mean | 0113 | 1837 | 1045 | 2124 | 4.95 | 2125 | 0548 | 1025 | 0236 | 2.79 |
| Median | 0314 | 1743 | 1115 | 2055 | 4.33 | 1959 | 0439 | 0946 | 0241 | 2.53 |
| SD | 0440 | 0239 | 0207 | 0122 | 2.55 | 0414 | 0242 | 0220 | 0314 | 1.04 |

All times are reported in relative clock time (hours) referenced from an average wake time of 0802 h. Amplitudes are reported in units of concentration.

**TABLE 3.** Times of the maxima and minima and amplitudes for $Ca_i$ of the individual fitted curves estimated from two harmonic regressions

| Subject | Baseline day | | | | | Constant routine | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | $t_{1\ max}$ | $t_{2\ max}$ | $t_{1\ min}$ | $t_{2\ min}$ | Amp | $t_{1\ max}$ | $t_{2\ max}$ | $t_{1\ min}$ | $t_{2\ min}$ | Amp |
| 1265V | 1844 | 0542 | 1133 | 0122 | 0.0947 | 1746 | 0359 | 1041 | 2322 | 0.0796 |
| 1273V | 0747 | | 1652 | | 0.1204 | 1202 | 0021 | 1818 | 0605 | 0.1267 |
| 1306V | 0649 | 1950 | 1342 | 0041 | 0.2133 | 1302 | | 2321 | | 0.2050 |
| 1310V | 1843 | 0243 | 1043 | 2302 | 0.1021 | 2151 | 1122 | 0440 | 1629 | 0.0844 |
| 1315V | 2011 | 0707 | 1336 | 0145 | 0.1641 | 1124 | 2345 | 1927 | 0320 | 0.1514 |
| Mean | 1426 | 0250 | 1317 | 0042 | 0.139 | 1513 | 0351 | 2005 | 0019 | 0.129 |
| Median | 1843 | 0412 | 1336 | 0101 | 0.120 | 1302 | 0210 | 1927 | 0121 | 0.127 |
| SD | 0633 | 0501 | 0222 | 0112 | 0.050 | 0428 | 0520 | 0638 | 0554 | 0.052 |

All times are reported in relative clock time (hours) referenced from an average wake time of 0802 h. Amplitudes are reported in units of concentration.

to document that a significant component of the daily PTH rhythm is endogenous.

The greater amplitude of cortisol, body temperature, and PTH rhythm on the baseline day than during the CR reflects the fact that a component of each of these rhythms is evoked by periodic environmental and behavioral stimuli, which are normally superimposed on an endogenous circadian component. It is also possible that a component of the PTH rhythm observed under the CR may reflect a remnant of the rhythm described under baseline conditions. To completely eliminate that possibility, a 3- to 5-day CR would be necessary, although that protocol would include significant sleep deprivation of the subjects.

It is unlikely that the circadian pattern for PTH during the CR is a reflection of the subjects' lower mean dietary calcium intake during that part of the protocol. Indeed, the circadian pattern for PTH in the two subjects who consumed diets with identical calcium contents during the baseline day and the CR was indistinguishable from the circadian rhythm for PTH for the whole study group.

The amplitude of the PTH rhythm is comparable to the amplitude of 4–5 pg/mL we estimated from the data collected in young women by Ledger *et al.* (12), but is slightly lower than that reported by several other researchers, averaging 7–10 pg/mL (4, 6, 15). Most studies have reported only one maximum for the PTH diurnal rhythm (2, 4, 7, 9), most often in the early morning hours (2, 4, 9), and have consistently identified a primary nadir that occurs at approximately 1000 h, as seen in our study (4, 6–9). More recent studies, however, have described a bimodal pattern (6, 8, 15) similar to our finding of two peaks for the PTH rhythm, with a major peak at 0314 h and a secondary peak at 1726 h.

Our analysis of $Ca_i$ levels is consistent with previous studies that reported variable times for peaks and troughs (6, 7, 8, 15, 19, 24). The conflicting results reported in these studies and the data collected in our five subjects suggest that diurnal $Ca_i$ patterns are probably not the primary determinant of the PTH circadian pattern. We cannot exclude the possibility, however, that another study, which includes a larger number of subjects and a more frequent blood-sampling schedule, may detect a consistent amplitude endogenous rhythm for $Ca_i$.

The diurnal rhythms for UCa/Cr, UNa/Cr, and $UPO_4$/Cr in our study confirm the results of other investigators, who have reported a nocturnal decrease for the former two minerals and an early morning drop for the latter (16, 25–27). The persistence of the circadian rhythm of UCa excretion during the CR protocol is consistent with recent data on mineral ion excretion collected when volunteers were subjected to minimal activity and given evenly spaced meals (27). Despite the fact that UNa excretion increases the urinary clearance of calcium, the $t_{max}$ for urinary sodium/Cr does not coincide

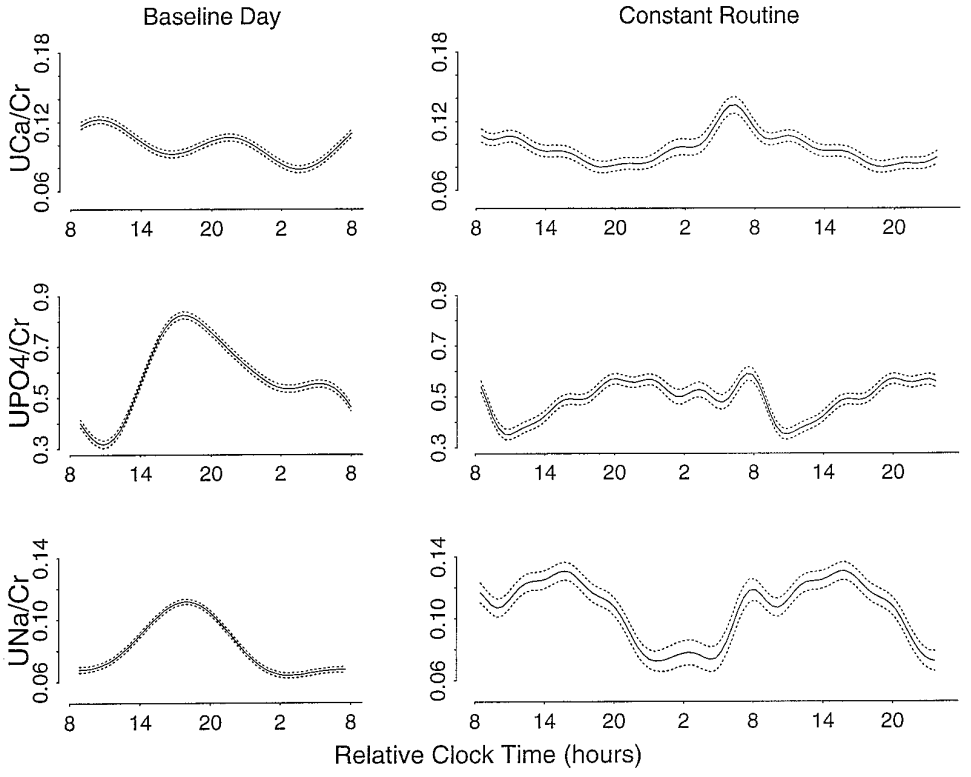


FIG. 2. Estimated population mean rhythm curves (±2 SD) for UCa/Cr, $UPO_4$/Cr, and UNa/Cr on the baseline day and during the CR. The population mean rhythm was estimated by harmonic regression fit to the pooled data from each individual subject's urinary electrolyte data measurements, normalized by urine creatinine. The error curves were constructed by computing pointwise 95% confidence intervals based on the population regression parameter estimates.

**TABLE 4.** Times of the maxima and minima and amplitude of urinary electrolyte levels

| Urine | Baseline day | | | | | Constant routine | | |
|---|---|---|---|---|---|---|---|---|
| | $t_{1\ max}$ | $t_{2\ max}$ | $t_{1\ min}$ | $t_{2\ min}$ | Amp | $t_{1\ max}$ | $t_{1\ min}$ | Amp |
| UCa/Cr | 1026 | 2130 | 0334 | 1639 | 0.0219 | 0611 | 1855 | 0.0273 |
| $UPO_4$/Cr | 1740 | 0520 | 1052 | 0243 | 0.2544 | 0735 | 1049 | 0.1205 |
| UNa/Cr | 1758 | 0723 | 0249 | 0830 | 0.0238 | 1545 | 0106 | 0.0295 |

All times are reported in relative clock time (hours) referenced from an average wake time of 0802 h. Amplitudes are reported in units of concentration.

with the $t_{max}$ for UCa/Cr, suggesting that it is highly unlikely that the rhythm of the former is driving that of the latter. PTH is a phosphaturic hormone that promotes calcium retention by the distal tubule. During the baseline day, phosphate excursion was at its highest when PTH levels displayed the smaller peak ($t_{2max}$). This can be explained by the fact that the $t_{2max}$ for PTH takes place when serum phosphate, and therefore the delivery of this mineral at the tubular level, was at its highest. This results in a greater $UPO_4$ excretion during the day than during the night, when PTH levels are at their highest but subjects are fasting. The negative correlations with time lag in UCa/Cr excretion and positive correlations with time lag in $UPO_4$/Cr with the increments in PTH levels are suggestive of a physiological role for the PTH circadian rhythm in regulating Ca and $PO_4$ excretion. Thus, the PTH circadian rhythm may be extremely important for urinary calcium conservation and the optimization of calcium balance. Indeed, in our study, the blunting of PTH rhythm during the CR was accompanied by enhanced urinary calcium excretion. Our data are consistent with those of Calvo *et al.* (6), which suggested that a delayed and blunted nocturnal increase in intact PTH in women may explain their greater rates of UCa excretion during the night.

The persistence of the PTH circadian rhythm during the CR protocol suggests that even though this rhythm may be modulated by external factors, it certainly is not solely dependent upon them. The circadian pacemaker resides in the suprachiasmatic nucleus of the hypothalamus in the brain. The calcium receptor gene that mediates calcium sensing by the parathyroid gland, which has been recently cloned by our group, is heavily expressed in certain areas of the brain (28, 29). This finding raises the intriguing possibility that circadian expression of this receptor centrally and peripherally (at the level of the parathyroid gland) may explain in part the circadian rhythm for PTH levels on both the baseline day and during the CR. Moreover, the same receptor that plays a major role in UCa handling is also expressed heavily in the thick ascending loop and distal convoluted tubules of the kidney, sites of PTH-regulated renal Ca handling (30).

In conclusion, our studies demonstrate that a large component of the PTH rhythm is endogenous. The PTH circadian rhythm may play an important role in calcium balance through effects on UCa retention. Alterations in its rhythm characteristics, including amplitude and phase, may result in

a catabolic calcium and bone-remodeling profile, thus contributing to the pathophysiology of osteoporosis.

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