Immediate effects of an 8-h advance shift of the rest-activity cycle on 24-h profiles of cortisol

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Caufriez, Anne, Rodrigo Moreno-Reyes, Rachel Leproult, Françoise Vertongen, Eve Van Cauter, and Georges Copinschi. Immediate effects of an 8-h advance shift of the rest-activity cycle on 24-h profiles of cortisol. Am J Physiol Endocrinol Metab 282: E1147–E1153, 2002; 10.1152/ajpendo.00525.2001.—To investigate the adaptation of plasma cortisol profiles to an abrupt phase advance of the rest-activity cycle, eight normal young subjects were submitted in a sleep laboratory to an 8-h advance shift of their sleep-wake and dark-light cycles. The shift was achieved by advancing bedtimes from 2300–0700 to 1500–2300. Blood samples were obtained at 20-min intervals for 68 consecutive hours. The shift resulted within 6–9 h in a 3- to 4-h advance of timings of the nadir of the cortisol profile and of the end of the quiescent period but had no immediate effect on the timing of cortisol acrophase. The quiescent period of cortisol secretion was shortened and fragmented. Thus a major advance shift achieved without enforcing sleep deprivation results in a rapid partial adaptation of the temporal profiles of cortisol but also in a marked disruption of the cortisol quiescent period. Sleep onset was consistently followed by a decrease in cortisol concentrations. Conversely, both sleep-wake and dark-light transitions were consistently associated with cortisol secretory pulses.

The 24-h profile of plasma cortisol in humans reflects the temporal organization of hypothalamic-pituitary-adrenal activity. This rhythm is primarily controlled by the circadian pacemaker, but the effects of sleep-wake transitions can be clearly identified (26). Sleep onset is frequently associated with a short-term inhibition of cortisol secretion, whereas in the second part of the night, awakenings are consistently associated with cortisol secretory pulses (2, 13, 18, 23, 28, 30). Furthermore, sleep loss results in an elevation of evening cortisol levels (9, 20). Therefore, abrupt time shifts of the rest-activity cycle, as during shift work rotations and jet lag, may have variable effects on 24-h cortisol patterns and will depend on the importance of the associated sleep deprivation.

Several studies have indicated that adaptation of the human circadian phase to a shifted schedule may be facilitated by adequately timed bright light exposure (17, 27). Because a recent study has indicated that cortisol secretion may be stimulated by photic inputs (8), it is possible that cortisol profiles may adapt faster to abrupt advance shifts of the rest-activity cycle when activity occurs in the presence of bright, rather than dim, light.

The present study was designed to investigate the effects on plasma cortisol profiles of an abrupt 8-h advance shift of the sleep-wake, rest-activity, dark-light, and feeding cycles achieved in a sleep laboratory by advancing bedtimes from 2300–0700 to 1500–2300, i.e., without enforcing sleep deprivation, and to evaluate the impact of bright light exposure. Plasma cortisol levels were determined at 20-min intervals for 68 consecutive hours, which included a 28-h baseline period and 40 h of postshift conditions, including two shifted sleep periods.

SUBJECTS AND METHODS

Subjects

Eight normal subjects [four women (subjects 1–4) and four men (subjects 5–8)], aged 21–33 yr, were selected after clinical and biological evaluation. The body weight for all subjects was in the normal range [body mass index: 21.9 ± 0.7 (SE) kg/m²]. They were nonsmokers, had no history of substance abuse, and had not taken any drug during the past 6 wk. Night and/or shift workers, subjects who had traveled across time zones during the 2 mo preceding the study, and subjects with sleep complaints or with personal history of endocrine, metabolic, psychiatric, or neurological disorders were excluded from the study. Female volunteers had normal ovulatory cycles and were studied at the midfollicular phase. None of them had received oral contraceptives for at least 6 wk before the study. Written informed consent was obtained from all volunteers. The study protocol was approved by the institutional review board.

The subjects spent two consecutive nights in the sleep laboratory 1 wk before the beginning of the investigation to

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habituate to the hospital environment and recording procedures. All subjects participated in three different studies (referred to as dim light, bright light, and zolpidem/dim light; see below) separated by at least 1 mo. The order of the studies was randomized. During the week preceding the first study and during the periods between the studies, the subjects were asked to maintain regular sleep-wake cycles (bedtime 2300–0700 in darkness) and meal schedules (breakfast 0800; lunch 1230; dinner 1900). The present report focuses on the results obtained in the dim light and bright light studies, i.e., in the studies performed without pharmacological sleep facilitation.

Experimental Protocol

In each of the two studies, the subjects were hospitalized in the sleep laboratory for four consecutive nights. A schematic representation of the experimental design is shown in Fig. 1. During the first night, which served as an additional habituation night, the subjects remained recumbent in total darkness from 2300 to 0700, and sleep was polygraphically recorded. Upon awakening, the subjects were maintained in the seated/upright position in dim light conditions (≥200 lux) until 2300, and no naps were allowed. A sterile heparin-lock catheter was inserted in the forearm at 1000 and, starting at 1100, 2-ml blood samples were obtained at 20-min intervals for 68 consecutive hours, which included successively 28 h in baseline conditions and 40 h in postshift conditions. The intravenous line was kept patent by a slow drip of heparinized saline. During the sleep period, the indwelling catheter was connected to plastic tubing extending to an adjoining room, as previously described (6).

During the baseline period, meals were served at 0800, 1230, and 1900. From 2300 to 0700, subjects remained recumbent in total darkness while sleep was polygraphically recorded.

The first shifted period started at 1500, when the subjects had to go to bed and were maintained recumbent in total darkness until 2300 while sleep was polygraphically recorded. At 2300, lights were switched on, and the subjects had to get up. Recumbency and naps were prevented during the scheduled 2300–1500-waking period. Subjects walked around the unit and were encouraged to read, listen to the radio, watch television, and chat with members of the staff. Breakfast, lunch, and dinner were served at 0000, 0430, and 1100, respectively. Thus the dark-light, sleep-wake, rest-activity, and feeding cycles were abruptly advanced by 8 h.

The second shifted period started the following day at 1500. The same dark-light, sleep-wake, rest-activity, and feeding cycles as during the first shifted period were maintained.

This protocol design was enforced in each of the two studies. In the dim light study, light intensity was maintained around 200 lux during all ambulatory periods, and the subjects were given a single oral dose of placebo 15 min before both shifted bedtime periods, i.e., at 1445. In the bright light study, the subjects were given a single oral dose of placebo 15 min before both shifted bedtime periods but were exposed to bright light of at least 2,000 lux during ambulatory hours on both shifted periods (i.e., from 2300 on day 2 until 1500 on day 3 and from 2300 on day 3 until the end of the study).

Sleep Analysis

Polygraphic sleep recordings were scored at 20-s intervals in stages wake, I, II, III, IV, and rapid-eye-movement (REM), using standardized criteria (14). Sleep onset and morning awakening were defined as, respectively, the times of the first and last 20-s intervals scored II, III, IV, or REM. The sleep period was defined as the time interval separating sleep onset from final morning awakening. The sleep latency was defined as the time interval from lights off until sleep onset. Sleep efficiency was calculated as the total recorded time minus the time spent awake, expressed as a percentage of the total recording time.

Hormonal Assays

Each blood sample was immediately centrifuged at 4°C. Plasma samples were frozen at −20°C until assay. Plasma cortisol levels were measured using the Gamma Coat Cortisol Kit (Clinical Assay, Cambridge, MA) with a low limit of sensitivity of 5 ng/ml, an average intra-assay coefficient of variation of <5%, and an interassay coefficient of variation of 10%. All samples from the same individual study were measured in the same assay.

Analysis of Cortisol Profile

The waveshape of each individual profile of plasma cortisol was quantified by a best-fit curve obtained by repeated periodogram calculations (21). The acrophases and nadirs were defined as, respectively, the times of occurrence of maxima and minima in the best-fit curve. The amplitude of the best-fit curve was defined as 50% of the difference between the value at the highest acrophase and the value at the lowest nadir and was expressed as a percentage of the overall mean level. The quiescent period of cortisol secretion was defined as starting (ending) when concentrations lower (higher) than 30 ng/ml were observed for at least three consecutive samples. The onset of the nocturnal cortisol circadian rise corresponds to the end of the quiescent period. Under baseline conditions, the quiescent period generally consists of a major interval centered around midnight and lasting 4–6 h without interruption. When fragmentation of the cortisol quiescent period was observed, the duration of the major uninterrupted interval was calculated. The timings of the cortisol nadir and of the onset of the circadian rise are thought to reflect the circadian rhythmicity, whereas the timing of the acrophase and the amplitude of the diurnal variation are influenced by sleep-wake transitions. Signifi-
cant pulses were identified and characterized using a previously described algorithm (ULTRA; see Ref. 22). A pulse was significant if both its increment and its decline exceeded, in relative terms, two times the intra-assay coefficient of variation in the relevant range of concentration. The increment of the pulse was defined as the difference between the level of the peak and the level at the preceding trough.

**Tests of Significance**

Effects of the study condition and of the time interval into the study (baseline, shifted period 1, shifted period 2) were evaluated by ANOVA for repeated measures. Comparisons of pulse amplitude in different conditions were evaluated by factorial ANOVA. All tests were performed using Statview SE+ (Abacus Concepts, Berkeley, CA) software for Macintosh computers. Unless otherwise indicated, all group values were summarized as means and SE.

**RESULTS**

**Cortisol Profiles**

**Dim light study.** Figure 2, top, shows the mean cortisol profiles observed during the study with dim light exposure. The individual cortisol profile of a representative subject during this dim light study is shown in Fig. 3. Summary measures quantifying cortisol profiles are given in Table 1.

**BASELINE.** During the baseline period, a normal 24-h pattern of plasma cortisol was observed in all individual profiles. Cortisol values declined progressively during the afternoon and the evening to reach a nadir at 2400 ± 35 min. In six of the eight subjects, the nadir was observed between 2340 and 0100, whereas it occurred at 2100 and 0300 in subjects 7 and 8, respectively. The nadir value averaged 17 ± 2 ng/ml. The onset of the quiescent period occurred at 1925 ± 51 min. This quiescent period consisted of a single episode in five of eight individual profiles. The single or the major uninterrupted quiescent episode lasted 5 h 58 ± 63 min. The end of the quiescent period was observed at 0250 ± 30 min, when the early morning cortisol circadian rise was initiated. Thereafter, cortisol levels rapidly increased to reach an acrophase at 0715 ± 15 min. The duration of the circadian rise averaged 4 h 25 ± 78 min. The acrophase value averaged 112 ± 5 ng/ml. The amplitude of the best-fit curve averaged 47 ± 3%.

The 24-h mean cortisol levels, estimated over the period 1100–1100, averaged 64.5 ± 3.9 ng/ml. A total of 10.5 ± 1.1 significant pulses occurred over that period. Pulse increments averaged 50 ± 7 ng/ml.

**ADAPTATION TO THE SHIFT: POSTSHIFT PERIOD 1.** The effects of the shift on various cortisol parameters are shown in Fig. 4, left. During the first postshift period, the cortisol nadir was advanced markedly compared with baseline conditions, with the shift averaging 3 h 20 ± 42 min ($P < 0.001$). Interestingly enough, no shift was observed in subject 7 (who had an early timing of the nadir during the baseline period), whereas the most important shift (6 h) was evidenced in subject 8 (who had a late timing of the nadir during the baseline period). On average, the nadir occurred at 2040 ± 27 min. The advanced timing of the nadir appeared to partly reflect the consistent occurrence of a large cortisol pulse at the end of the first shifted sleep period (see below). The quiescent period was therefore prematurely terminated at 2327 ± 52 min, i.e., on average 3 h 23 ± 39 min earlier than under baseline conditions ($P < 0.001$).

In contrast, no shift was observed for the acrophase, which occurred at the same time (0710 ± 24 min) as under baseline conditions. Thus the duration of the rising phase of cortisol secretion was increased by nearly 3 h, averaging 7 h 23 ± 137 min ($P < 0.003$). This rising phase assumed a biphase pattern, contrasting with the monotonic elevation observed under baseline conditions. The onset of the quiescent period, which occurred at 1755 ± 32 min, was advanced only by 1 h 18 min ± 64 min, and this shift failed to reach significance at the group level. Because the offset, but not the onset, of the quiescent period was advanced
significantly, the duration of the quiescent period was reduced. It consisted of a single episode in four of eight individual profiles. The single or the major uninterrupted quiescent episode lasted only 3 h 20 ± 30 min, i.e., almost 50% less than in the baseline period (P < 0.03).

The 24-h mean cortisol levels (69.5 ± 5.2 ng/ml) and the nadir value (23 ± 3 ng/ml) were increased slightly compared with baseline values, but these differences failed to reach significance. The acrophase value and the amplitude of the circadian variation were essentially unchanged. Similarly, there were no changes in pulse frequency and amplitude.

**ADAPTATION TO THE SHIFT: POSTSHIFT PERIOD 2.** During the second postshift period, there was only a minor trend to further adaptation of the cortisol profiles (Fig. 4, left). There was no further advance of the timing of the nadir and only a minor (<30 min) further advance of the onset of the quiescent period. This quiescent period consisted of a single episode in five of eight individual profiles. However, a further shift of almost 1 h was observed for the end of the quiescent period, which occurred at 2235 ± 62 min, i.e., 4 h 15 min earlier than during the baseline period. The single or the major uninterrupted quiescent episode lasted only 2 h 58 ± 41 min, i.e., 3 h less than in the baseline period (P < 0.02). The nadir value averaged 25 ± 3 ng/ml, i.e., an increase of nearly 50% from baseline levels (P < 0.05). Pulse frequency and amplitude were not altered.

**Bright light study.** Bright light exposure had no effect on cortisol profiles compared with dim light exposure. Thus 24-h mean cortisol levels, nadir and acrophase values, amplitude of the circadian variation, timings of nadir and of acrophase, timing and duration of the quiescent period, pulse frequency, and amplitude were all similar in the bright light and in the dim light studies (Fig. 2, bottom).

**Effects on Cortisol Levels of Sleep-Wake and Dark-Light Transitions**

Sleep parameters recorded during these studies have been reported previously (7). Briefly, sleep parameters were normal for laboratory conditions during the baseline period: in the dim light study, sleep latency averaged 19 ± 3 min (range: 8–35 min), and sleep efficiency averaged 83 ± 2%. During the first shifted night, sleep latency was unchanged (18 ± 4 min; 3–44 min), but sleep efficiency was reduced markedly, averaging 50 ± 7%, with a very wide range of individual values (27–80%; P < 0.001). This reduction reflected decreases in stages I and II, stages III and IV (slow wave), and REM. During the second shifted night, sleep latency dropped to 9 ± 2 min (P < 0.05), and sleep efficiency improved compared with the first shifted period, averaging 71 ± 5%. Bright light exposure had beneficial effects during the second shifted night: sleep efficiency averaged 82 ± 4% (P < 0.05 vs. dim light). The present section will focus on the effects of sleep-wake and dark-light transitions on cortisol secretion.

Sleep onset-associated inhibition of cortisol levels. Possible decreases in plasma cortisol values after sleep onset at habitual bedtime (around 2300) are difficult to evidence because of the already preexisting low evening levels. Therefore, the relations between sleep onset and cortisol profiles were investigated only during the postshift periods. After sleep onset, plasma cortisol levels dropped in all of the 32 individual profiles obtained during both shifted periods in the two treatment conditions. The magnitude of the decrease was estimated within the next 120 min. This decrease was highly significant for both shifted nights in both experimental conditions (P < 0.001). The magnitude of the decrease was quite similar during both shifted periods and in the two treatment conditions, averaging 45 ± 7 ng/ml or 53 ± 3% from the presleep level.

Cortisol pulses associated with transient awakenings. In the 16 individual profiles obtained under baseline conditions, a total of 12 transient awakenings were investigated only during the postshift periods. After sleep onset, plasma cortisol levels dropped in all of the 32 individual profiles obtained under baseline conditions in both treatment groups. Possible decreases in plasma cortisol values after sleep onset at habitual bedtime (around 2300) are difficult to evidence because of the already preexisting low evening levels. Therefore, the relations between sleep onset and cortisol profiles were investigated only during the postshift periods. After sleep onset, plasma cortisol levels dropped in all of the 32 individual profiles obtained during both shifted periods in the two treatment conditions. The magnitude of the decrease was estimated within the next 120 min. This decrease was highly significant for both shifted nights in both experimental conditions (P < 0.001). The magnitude of the decrease was quite similar during both shifted periods and in the two treatment conditions, averaging 45 ± 7 ng/ml or 53 ± 3% from the presleep level.

**Table 1. Cortisol parameters during the dim light study**

<table>
<thead>
<tr>
<th></th>
<th>Baseline Period</th>
<th>First Shifted Period</th>
<th>Second Shifted Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>24-h Mean cortisol, ng/ml</td>
<td>64.5 ± 3.9</td>
<td>69.5 ± 5.2</td>
<td>63 ± 3</td>
</tr>
<tr>
<td>Nadir value, ng/ml</td>
<td>17 ± 2</td>
<td>23 ± 3</td>
<td>25 ± 3*</td>
</tr>
<tr>
<td>Acrophase value, ng/ml</td>
<td>112 ± 5</td>
<td>115 ± 8</td>
<td>115 ± 8</td>
</tr>
<tr>
<td>Circadian amplitude, %mean</td>
<td>47 ± 3</td>
<td>46 ± 4</td>
<td>46 ± 4</td>
</tr>
<tr>
<td>Nadir timing, clocktime ± min</td>
<td>2400 ± 35</td>
<td>2040 ± 27†</td>
<td>2035 ± 33†</td>
</tr>
<tr>
<td>Acrophase timing, clocktime ± min</td>
<td>0715 ± 15</td>
<td>0710 ± 24</td>
<td>0710 ± 24</td>
</tr>
<tr>
<td>QP onset, clocktime ± min</td>
<td>1925 ± 51</td>
<td>1755 ± 32</td>
<td>1813 ± 49</td>
</tr>
<tr>
<td>QP offset, clocktime ± min</td>
<td>0250 ± 30</td>
<td>2327 ± 52†</td>
<td>2235 ± 62†</td>
</tr>
<tr>
<td>Major QP duration, min</td>
<td>358 ± 63</td>
<td>200 ± 30</td>
<td>178 ± 41§</td>
</tr>
<tr>
<td>Pulse frequency, pulses/24 h</td>
<td>10.5 ± 1.1</td>
<td>10.1 ± 1.5</td>
<td>10.5 ± 0.5</td>
</tr>
<tr>
<td>Pulse amplitude, ng/ml</td>
<td>50 ± 7</td>
<td>53 ± 5</td>
<td>55 ± 5</td>
</tr>
</tbody>
</table>

Values are means ± SE. QP, quiescent period. *P < 0.05, †P < 0.001, §P < 0.03 and ¶P < 0.02 compared with baseline period.
lastring at least 10 min were recorded. All were followed within the next 20 min by a significant cortisol pulse. A total of 40 such awakenings occurred during postshift periods 1 and 2, and 15 (38%) were followed by a significant pulse within the next 20 min, regardless of the period and treatment condition.

Cortisol pulses associated with final awakenings and dark-light transitions. Under baseline conditions, final morning awakening occurred in 13 of the 16 individual profiles <20 min (i.e., one sampling interval) before lights were turned on and was followed within the next 20 min by a significant pulse in all of the 13 profiles. In three profiles, final morning awakening occurred between 0544 and 0615, and a pulse was observed within the next 20 min in two profiles while the subjects were still recumbent in continuous darkness. In all of these three profiles, a second pulse also occurred when the lights were turned on at 0700.

During the first postshift period, final awakening occurred <20 min before lights were turned on in six individual profiles in the dim light study and in five individual profiles in the bright light study. In all of these 11 profiles, final awakening was followed within the next 20 min by a significant pulse. In two profiles obtained under dim light conditions and three profiles obtained under bright light conditions, final awakening occurred between 1814 and 2221, and a pulse was evidenced within the next 20 min in all of them while the subjects were still recumbent in continuous darkness until 2300. A pulse was also observed when the lights were turned on in one of the two dim light profiles and in two of the three bright light profiles.

During the second postshift period, final awakening occurred <20 min before lights were turned on in six “dim light” profiles and in all of the eight “bright light” profiles. It was followed within the next 20 min by a significant pulse in 13 of these 14 profiles. In one dim light profile, final awakening occurred at 1900 and was followed by a pulse within the next 20 min and by another pulse when the lights were turned on. In another dim light profile, no pulse was observed after final awakening, which occurred at 2230, but a pulse was evidenced when the lights were turned on at 2300.

The amplitude of sleep-wake- and/or dark-light-associated cortisol pulses appeared to be unaffected by the study period or the treatment condition. In total, across all periods and treatment conditions, final awakenings were concomitant with dark-light transitions on 38 occasions, and associated cortisol elevations averaged 92 ± 7 ng/ml. On 10 occasions, final awakening occurred at least 30 min before the lights were turned on, and associated cortisol elevations were significantly lower (P < 0.01), averaging 48 ± 11 ng/ml. In the same 10 profiles, cortisol elevations associated with dark-light transitions occurring when the subjects were already awake averaged 73 ± 20 ng/ml.

DISCUSSION

Adaptation of the human circadian rhythmicity to an abrupt phase advance, as occurs in eastward jet lag or advance work shift rotation, is usually considered to be more difficult than adaptation to a phase delay of similar magnitude (1), because the endogenous circadian period is slightly longer than 24 h (4). The present data indicate that an abrupt 8-h advance of the sleep-wake, dark-light, rest-activity, and feeding cycles achieved without enforcing sleep deprivation resulted within 6–9 h in a 3- to 4-h advance of the timing of the nadir and of the end of the quiescent period. The timing of the cortisol nadir and the end of the quiescent period have been used as related markers of the circadian phase in a number of previous studies (3, 6, 10, 24). Under the present conditions, however, the apparent phase advance of these phase reference points is more likely to partly reflect effects of robust cortisol pulses associated with sleep-wake and/or dark-light transitions rather than to be caused solely by a large rapid shift of the endogenous circadian phase. Consistent with this interpretation, another robust marker of the circadian phase, the melatonin onset, was shifted by <2 h under the same experimental conditions (25 and Fig. 4, right). Thus approximately one-half of the phase advance of the nadir and of the end of the quiescent period may reflect an advance of the circadian phase.
whereas the other one-half would represent effects of awakenings from shifted sleep.

In contrast to the advance of the nadir and the end of the quiescent period, the timing of the cortisol acrophase was not changed after the abrupt 8-h advance of the sleep-wake cycle. The biphasic nature of the cortisol rise after the shift suggests that the increase in cortisol secretion associated with sleep-wake and/or dark-light transitions resulted in a delay of the subsequent circadian rise and prevented any adaptation of the acrophase to the new schedule.

The lack of adaptation of the acrophase and the advance of the cortisol rise were reflected in the shortening and fragmentation of the quiescent period, and plasma cortisol levels were elevated at the time of the usual trough of the rhythm. These disruptions, which were more pronounced during the second shifted period than immediately after the shift, probably represent the deleterious consequences of the time shift. Indeed, even modest elevations of plasma cortisol levels at the time of the usual trough of the rhythm are thought to facilitate the development of central and peripheral disturbances associated with glucocorticoid excess, such as insulin resistance (5, 12) and memory deficits resulting from impaired hippocampal function (11). Animal studies have indicated that increased citis resulting from impaired hippocampal function de

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riod than immediately after the shift, probably repre-

sent the deleterious consequences of the time shift.

The biphasic rise of plasma cortisol secretion associated with sleep-wake and/or dark-light transitions in stimulating cortisol secretion, even when it occurs in continuous darkness, but the cortisol elevation is enhanced by increasing light intensity (16). Most recently, it was shown that the transition from dim to bright light in the early morning but not in the afternoon induces an immediate elevation of cortisol levels in subjects maintained continuously awake (8). The present results indicate that the transition from darkness to dim light may also stimulate cortisol secretion in subjects who are awake. When sleep-wake and dark-light transitions occurred concomitantly, associated cortisol elevations were nearly two times as high as when the sleep-wake transition occurred in continuous darkness.

Although the present data emphasize the role of dark-light transitions in stimulating cortisol secretion, they also indicate that the transition from darkness to bright light had no additional effects compared with the transition from darkness to dim light. It is likely that the 16-h period of bright light exposure overlapped both the phase-advance and the phase-delay portions of the human phase-response curve to light and therefore resulted in a zero net shifting effect.

In conclusion, the present study indicates that exposure of normal young subjects to an abrupt 8-h advance of the sleep-wake and dark-light cycles achieved without enforcing sleep deprivation results in a rapid partial adaptation of the temporal profiles of cortisol but also in a marked disruption of the cortisol quiescent period. Adaptation is not facilitated by bright light exposure. The present results also show the importance of both sleep-wake and dark-light transitions in the modulation of hypothalamic-pituitary-adrenal activity.

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