

# Neuroendocrine profiles in mood disorders

Paul Linkowski

Sleep Laboratory, Department of Psychiatry, Hôpital Erasme, Université Libre de Bruxelles, Belgium

## Abstract

The study of neuroendocrine abnormalities in major mental illness, such as the unipolar and bipolar affective syndromes, has been the focus of interest in the past few years. The neuroendocrine 'window' into the brain has been considered as a fruitful and promising approach to the study of mental disorders, as suggested by studies of some neuroendocrine challenge tests in depression that demonstrated their potential use as biological markers. The modern approach to hormonal dynamics focuses on the circadian and pulsatile profiles that truly represent physiological modulation and tests the hypothesis that an abnormality in circadian rhythms is present in affective illness. From the fundamental point of view, such studies performed using a frequent sampling interval over the 24-h cycle aim to clarify the control and significance of the temporal sleep and wake fluctuations of neuroendocrine system activities. Twenty-four-hour hypersecretion of cortisol, diurnal hypersecretion of growth hormone, and normal 24-h levels of prolactin have been reported in careful chronobiological studies of depressed patients, along with sleep recordings. In addition, a nocturnal quiescent period, and a subsequent increase towards the morning maximum, have been consistently found in a subset of depressed patients suffering from endogenous depression. After successful treatment with antidepressants, most of these abnormalities (with the exception of those found in the prolactin study) tend to correct. The normalization of the timing of hormonal secretion was accompanied by a correction of sleep abnormalities and in particular, a lengthening of the REM latencies. Normalization of cortisol secretion was associated with a decrease in the magnitude of episodic cortisol pulses whereas normalization of growth hormone secretion was due to a diminished number of secretory pulses. In conclusion, a disorder of circadian time-keeping seems to characterize acute episodes of major endogenous depression in some patients. This abnormality as well as the associated increases in adrenocorticotrophic and somatotrophic activities seem to be a state-, rather than trait-dependent phenomenon.

Received 28 July 2002; Reviewed 29 October 2002; Revised 6 January 2003; Accepted 12 February 2003

**Key words:** Chronobiology, cortisol, depression, growth hormone, neuroendocrinology.

## Introduction

The study of circadian profiles of pituitary hormones and of cortisol is of major importance for the clarification of the characteristics of the human circadian clock and also to test the hypotheses about the possible chronobiological disturbances in mental disorders, mainly in affective illness. In particular, Wehr and Wirz-Justice (1982) suggested that in depressed patients, an early timing of some circadian rhythms might be present during acute episodes of depression.

Neuroendocrine studies will be reviewed in the present paper with special emphasis on circadian studies which included concomitant sleep measurements

and, when possible, cross-sectional and longitudinal designs.

## Methodology of hormonal circadian studies

A rigorous and biomathematically sound methodology is mandatory for circadian studies. Requisites are as follows: if the quality of sleep is anticipated to play an important role in determining the nocturnal hormonal profile, study subjects should spend at least three nights of habituation in the study unit prior to the investigation.

To obtain valid estimation of the circadian and pulsatile endocrine parameters, it is necessary to sample at intervals not exceeding 20 min. Indeed, the pulsatile pattern of hormonal release may confound the estimation of the circadian rhythm characteristics if the sampling is less frequent (Van Cauter, 1981).

The sampling procedure (preferably at 15 min intervals) is generally started 1 h after catheter insertion

Address for correspondence: Dr P. Linkowski, Sleep Laboratory, Department of Psychiatry, Erasme Hospital, 808 route de Lennik, B-1070, Brussels, Belgium.

Tel.: 32-2-555.37.41 Fax: 32-2-555.69.55

E-mail: Paul.Linkowski@ulb.ac.be

and lasts for 25 h. Data collected during the first hour of sampling are discarded to avoid artifactual effects related to the venepuncture stress.

During the night, the catheter is connected to plastic tubing that extends to an adjacent room and sampling is performed without disturbing the subject. Naps are forbidden; during bedtime hours, the lights are turned off. The descriptions of these techniques have been published elsewhere (Linkowski et al., 1985, 1998).

### Quantifying circadian variations

To determine rhythm parameters in biological time, hormonal profiles and sophisticated biomathematical procedures are often necessary. For example, one procedure described below (Van Cauter, 1979; Linkowski et al., 1987), requires computer programs for circadian rhythm analyses, the so-called 'periodogram method'. The procedure for detecting and estimating circadian variations is based on periodogram calculations. These calculations consist of fitting a series of sinusoidal components on the series of data and of selecting those that fit significantly to the observed variation.

The significant components are added up to obtain the asymmetrical best-fit curve and superimposed on the experimental data. Maximum and minimum prints of the best-fit curve are often referred to as the 'acrophase' and the 'nadir' respectively. The amplitude of the rhythm may be estimated as 50% of the difference between the acrophase and nadir. It is important to point out that group characteristics should be derived from the analysis of individual profiles rather than the mean of individual data.

Indeed, calculating the transverse mean to illustrate group results must demonstrate the prior existence, in each individual profile or at least in the large majority of profiles, of the same characteristics as those shown by the transverse mean.

### Quantifying pulsatile variations

A variety of quantitative methods for the study of pulsatile variations has been proposed since the first systematic approach by Santen and Bardin (1973). The general principle of our method (see Van Cauter, 1988), the ultra algorithm, is briefly outlined here. This procedure is based on the general principle of a pulse by pulse evaluation of significance with respect to assay precision. Accordingly the principle of the ultra algorithm is the elimination of all peaks for which either the increment (difference between the peak and the preceding trough) or the decrement (difference between the peak and the next trough) does not exceed

a certain threshold related to the measurement error of the assay. The ultra algorithm has been proven to be of the same performance as other peak detection algorithms currently used (Urban et al., 1988).

### Cortisol circadian profiles

The most widely used marker of the human circadian clock is the 24-h profile of plasma cortisol because of the large amplitude of its circadian variation and its remarkable reproducibility. It is referred to as a 'paradigm' for human circadian rhythms (Copinschi et al., 2000). The 24-h cortisol profile shows an early morning maximum, declining levels throughout the day, a quiescent period of minimal secretory activity around midnight, and an abrupt elevation during late sleep. During the 24-h span, an average of 15 significant secretory pulses can be detected. The quiescent period of cortisol secretion typically extends from 22:00 to 02:00 hours whereas the acrophase occurs between 06:00 and 10:00 hours.

Experimental and theoretical evidence suggests that the episodic nature of cortisol secretion ultimately results from the intermittent activity of the hypothalamic pulse generator and that circadian signals modulate pulse amplitude rather than pulse frequency (Van Cauter et al., 1990; Veldhuis et al., 1989).

Twin studies have also shown that a genetic control is present for the timing of the nocturnal nadir of cortisol while environmental effects were detected for the 24-h mean and the timing of the nocturnal acrophase (Linkowski et al., 1993).

### Cortisol profiles in major depression

Hypersecretion of cortisol is found in a majority of severely depressed patients with endogenous features. Early studies have compared cortisol profiles in depressed psychotic patients and in normal controls (Sachar et al., 1973). The hypothesis that an early timing of certain circadian rhythms may be involved in the pathophysiology of endogenous major depressive illness has been discussed by Wehr and Wirz-Justice (1982).

Because variations of plasma corticotropin (ACTH) and cortisol are considered a good paradigm for human circadian rhythms, several studies explored extensively the nyctohemeral profiles of plasma cortisol in depressed patients. Jarrett et al. (1983) studied 14 patients with a primary major depressive illness and compared them to 14 age- and sex-matched healthy control subjects. In this study, the nadir of the nocturnal plasma cortisol concentration was significantly

greater in the group of depressed patients. Furthermore, the nocturnal increase in the plasma cortisol concentration occurred significantly closer to sleep onset in these patients, thus suggesting that adrenal activity increased earlier in depressed subjects than in normal subjects. Some of the disturbances seemed to persist in clinically euthymic patients.

In an extensive study of 32 endogenously depressed patients and 72 normal controls, Halbreich and his group (1985a,b) found that endogenously depressed patients had significantly higher mean 24-h plasma levels of cortisol than normal controls. In addition, the cortisol nadir of depressed patients was 40 min earlier than of normal subjects. However, when controlled for age, the difference between the normal subjects and the depressives was insignificant ( $p=0.15$ ). Interestingly, the first nocturnal secretory episode of cortisol started significantly earlier in depressed patients; this significance remained. These data suggest that some endogenously depressed patients might have an altered relationship between the circadian rhythm of cortisol and sleep.

In the same year, we reported extensive studies of circadian and pulsatile variations of plasma ACTH and cortisol levels in 18 men suffering from severe major endogenous depressive illness (8 unipolar and 10 bipolar) as well as in age-matched normal men (Linkowski et al., 1985). We found that the classical circadian variation of cortisol levels (i.e. morning, acrophase, progressive decline through the afternoon followed by a quiescent period) was present in all normal subjects and depressed patients. This circadian variation of cortisol paralleled a similar rhythm of ACTH levels in all controls and in 75% of the depressed patients. In normal subjects, the timing of the nocturnal nadir appeared as a function of age, the coefficient correlation between age and the time of occurrence of the nocturnal nadir being  $-0.90$  ( $p<0.02$ ). A significant advance ( $p=0.015$ ) of the cortisol and ACTH rhythms was found in unipolar depressed patients, regardless of age; it was also present in several patients with bipolar depression, but did not reach significance at the group level. In addition, the relative amplitude of the circadian rhythm of cortisol was significantly reduced ( $p<0.01$ ). When the pulsatile parameters were investigated, it was found that hypercortisolism in depressed patients was associated with an increased magnitude, but not the number of cortisol secretory episodes.

These findings support the hypothesis that, at least in a subset of the depressed major depressives, specific disturbances of the pituitary–adrenal axis and its temporal organization might be found. Furthermore, in

this subset of patients a chronobiological abnormality consisting of an early timing of cortisol rhythms might characterize the pathophysiology of depressive illness.

Other groups have subsequently explored possible disturbances in cortisol profiles in major depressive illness. Among them, Pfohl et al. (1985) studied the patterns of plasma corticotropin and cortisol concentrations in 25 depressed patients and 21 normal control subjects. Among the depressed patients, 8 were dexamethasone non-suppressors and 11 were suppressors. Before taking dexamethasone, depressed patients reached a daily nadir of cortisol concentration approx. 2 h earlier than did normal control subjects, reflecting an earlier initiation of the daily hypothalamo-pituitary rhythm. However, in this particular study, sleep was not monitored and the confounding effect of sleep abnormalities could not have been taken into account.

Additional extensive studies in this field were performed by Rubin et al. (1987). In one study, they examined cortisol circadian serum patterns, cortisol response to dexamethasone and 24-h urinary free cortisol before and after dexamethasone administration in 40 patients with primary definite endogenous depression diagnosed by research diagnostic criteria and in 40 individually matched normal control subjects (sleep was not controlled in this protocol). The patients who were dexamethasone escapers had higher serum cortisol levels at almost all times during the 24-h cycle.

Cortisol nadir was calculated as the mean of the three lowest sequential nocturnal values. The amplitude was calculated as the difference between the mean of the three highest morning cortisol values and the nocturnal nadir. In this study, the amplitudes of the cortisol rhythm were similar for all three groups (dexamethasone suppressors, dexamethasone non-suppressors and controls) as were the nadirs and the times of onset of the nocturnal rise.

Another set of interesting results comes from the group of Sou ete et al. (1985, 1989) in their studies of 18 depressed endogenous patients compared to age- and sex-matched controls. These patients showed clear circadian rhythm abnormalities along with a clear-cut hypercortisolism during the depressed state. No significant difference was found in the cortisol nadir between depressed and control subjects. Depressed patients showed a reduced amplitude of cortisol rhythm. This amplitude reduction was significantly correlated with the patients' Hamilton depression scores ( $p<0.05$ ).

Finally, more recently, Posener et al. (2000) showed that the amplitude of the 24-h cortisol profile was

reduced in depressed outpatients but no evidence for abnormal phase position of cortisol who present. Interestingly, abnormal cortisol profiles were also observed in manic patients (Linkowski et al., 1994) but not in schizophrenic patients.

### Cortisol profiles during antidepressant treatment

The effect of antidepressant treatment and clinical remission on cortisol circadian profiles has been explored in several studies. Plasma ACTH and cortisol concentrations were evaluated in 11 men suffering from major depressive illness during an acute episode of depression and during clinical remission following antidepressant treatment with either electroconvulsive therapy or amitriptyline (Linkowski et al., 1985). In agreement with previous reports from our group (before treatment), during the acute phase of the illness, the patients had abnormally short REM latencies, hypercortisolism (both during wake-time and during sleep), early timings of the nadirs of the ACTH-cortisol rhythms, shorter nocturnal periods of quiescent cortisol secretion and decreased amplitude of the cortisol circadian rhythm. The most common sleep abnormalities during the depressed state were increased amount of time spent awake, decreased amount of slow-wave sleep, and shortened REM latency.

Successful treatment resulted in a correction of these abnormalities, such that the distribution of sleep stages in the depressed patients did not differ from normal subjects. With regard to the cortisol parameters, after treatment the cortisol concentration returned to normal (a small decline in 24-h mean ACTH values after treatment did not reach significance but post-treatment values did not differ from normal values).

When expressed as a percentage of the 24-h mean, the rhythm amplitude was significantly increased after treatment, with post-treatment values in the normal range. The nadir of cortisol concentration was clearly delayed after treatment, resulting in a normal rhythm. During clinical remission after treatment, the magnitude of the secretory pulses was reduced compared to pretreatment values.

In a similar study, Steiger et al. (1989) explored sleep electroencephalogram (EEG) and the nocturnal secretion of cortisol concomitantly during acute depression before treatment and after recovery in 12 male patients with major depression (no normal subjects were studied). They found that sleep EEG disturbances during the acute phase of the illness persisted after recovery and the elevated nocturnal cortisol secretion observed before treatment was normalized

(independently from the sleep structure) after clinical remission.

Sou tre et al. (1985) also reported that successful antidepressant treatment normalized the 24-h cortisol profiles in depressed patients, in particular increasing the amplitude of the rhythm that was significantly decreased during acute state of depression.

Taken together, these numerous observations consistently indicate that major depressive illness is associated with disturbances in the circadian profiles of plasma cortisol, consisting of a hypercortisolism, produced by an enhanced release of cortisol with each secretory pulse and, also, a reduced amplitude of cortisol rhythm.

At least in a subset of severely depressed patients, a disturbance in temporal organization might also be present, consisting in advance of the ACTH and cortisol rhythm nadir and supporting the hypothesis that an early timing circadian rhythm characterizes some forms of major depressive illness. The increases in adrenocorticotrophic activity as well as the associated chronobiological abnormalities seem to be state- rather than trait-dependent.

### The 24-h profiles of growth hormone (GH) in depression

In man, the 24-h profile of plasma GH levels is usually considered to be dependent primarily on sleep (Van Cauter, 2000). In normal subjects, this profile is characterized by a major secretory event which is a spike occurring after sleep onset, in association with the first phase of slow-wave sleep. Other GH pulses may occur in later sleep and during wakefulness with a consistent temporal coincidence between nocturnal GH secretion and delta sleep (Van Cauter et al., 2000).

In the same sample of depressed patients as described above, 24-h plasma GH concentrations together with polygraphic recordings of sleep were studied in 16 major depressed men and in 8 age- and sex-matched controls. In this study, men with unipolar and bipolar depression secreted more GH than normal men. During sleep, depressed men and normal controls secreted similar amounts of GH despite an overall reduction in slow-wave stages in depressed men. The increased daytime secretion of GH was primarily due to an increase the number of GH spikes.

An early sleep GH increase was found in all but one of the normal men, was absent in all but one unipolar depressed men in this sample of the patients who had instead a presleep increase of GH (no such presleep peak was found in bipolar depressed patients) (Mendlewicz et al., 1985).

After treatment and clinical remission (Linkowski et al., 1987), the amount of GH secreted during wakefulness decreased to normal values, with fewer significant GH peaks. Furthermore, the major elevation of GH secretion in the early part of the night occurred later than during the depressive episode.

Three other neuroendocrine investigations explored the circadian and/or sleep-related GH secretion in depression. Jarrett et al. (1990) measured GH secretion during EEG-monitored sleep in 38 depressive patients and 35 normal controls. Before treatment, depressed patients had a significant reduction in GH secretion during sleep. Unexpectedly, no significant increase in GH secretion occurred during sleep after recovery from a depressive illness (this reduction in GH persisted even though a significant increase in the length of the first non-REM period was observed). These authors suggested that the observed reduction, which persisted throughout treatment and recovery into the drug-remitted state, might be a trait marker in patients with a recurrent depressive disorder (Jarrett et al., 1990).

In another study, Steiger et al. (1989) conducted a sleep-neuroendocrine evaluation among 10 unmedicated male patients with major endogenous depression during their depressive episode and following full clinical remission and drug-free state. No significant differences were found between GH nocturnal secretion before and after successful antidepressant treatment (diurnal GH values were measured).

Rubin et al. (1990) explored nyctohemeral GH profiles in 40 depressed patients in an age- and sex-controlled study. Compared with controls, patients showed no difference in basal nocturnal GH concentrations. Among depressed patients, those with more severe depressed mood had lower nocturnal GH secretion (sleep EEG recordings were not performed).

In conclusion, although diurnal hypersecretion has been described in depressed patients, this neuroendocrine abnormality has not been confirmed. On the other hand, conflicting results were also seen for nocturnal GH secretion, normal or decreased values being reported by some groups.

### The 24-h profiles of prolactin

In normal men, the 24-h profile of prolactin profiles has a bimodal pattern, with low concentrations around noon, an afternoon phase of augmented secretion and a major nocturnal elevation (acrophase) starting after sleep onset and culminating around mid-sleep.

Earlier reports on the 24-h profile of prolactin secretion in depressed patients have suggested that an

advance of the nocturnal prolactin elevation may characterize some forms of depressive illness (Halbreich et al., 1979). In a subsequent report (Linkowski et al., 1989), it was shown that during the acute phase of the illness unipolar depressed patients had fragmented patterns of prolactin secretion with an early timing of the nocturnal secretory phase of prolactin that started on average 2 h earlier than in normal subjects. The amplitude of prolactin 24-h profile was also reduced in these unipolar patients with subnormal prolactin levels occurring during the mid-sleep period. The antidepressant treatment, in contrast to the disturbances of the corticotropic and somatotrophic axes, did not consistently correct the abnormalities in the patterns of prolactin release observed during the acute phase of the illness. Altogether, these results might suggest that an early timing of nocturnal prolactin secretion and damping of the night-time prolactin elevation might be found in endogenously depressed patients. In a similar study, Rubin et al. (1989a) did not note major differences in nycthemeral prolactin levels in depressed men or woman (sleep was not recorded in this study).

The further report by Jarrett et al. (1987) of normal prolactin secretion during sleep might not be at variance with our findings because these authors restricted their comparative analysis to the first 180 min of sleep whereas the damped prolactin secretion demonstrated in our study was significant only in sleep onset and 360 min after the sleep onset.

Results from these studies suggest thus that, in patients suffering from depressive illness, normal overall prolactin levels are present whereas chronobiological abnormalities consisting of an early timing by the nocturnal prolactin rise may be present in unipolar depressed patients.

### Conclusions

The study of 24-h neuroendocrine profiles in depressive illness has a major heuristic value in the study of the physiopathology of affective disorders. The study of these neuroendocrine rhythms is however very considerable and only very few neuroendocrine circadian studies have been published in the last five years. However, a large amount of studies has documented several endocrine aberrations in patients with depression. Detailed experimental studies of the characteristics of various 24-h pituitary and adrenal hormones allowed for the testing of various chronobiological hypotheses about abnormal circadian rhythm and characterization of the relationship of the timing and structure of sleep in depression. When

present, these abnormalities appear to be 'state' (i.e. episode related) rather than trait (i.e. lifetime) dependent. This further suggests that a least a subgroup of depressed patients have documented abnormalities in the circadian clock. It may also be hypothesized that 24-h rhythm abnormalities in major depression may be due to altered clock genes. Further long-term prospective studies are needed to assess the stability of these chronobiological dysregulations and to study the effect of various antidepressant treatments on the resynchronization of biological rhythms.

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