54. Circadian Rhythm Disturbances in Affective Disorders: Facts and Fictions

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The cycling nature of affective disorders has put these psychopathological conditions into the focus of medical chronobiology. However, our knowledge is still rather limited in this respect, and too often casual observations and theoretical speculations are accepted as proving profound disturbances of biological (above all, circadian) rhythms in these disorders. It is our intention to evaluate critically the present state of knowledge in this field in order to disentangle proved facts from mere fictions. Particular reference is made to carefully designed observations of affectively ill patients in a time-cue-free environment, as they provide the only solid basis for conclusions regarding the endogenous component of biological rhythms. Only those hypotheses are discussed that have drawn most attention in chronobiological research to affective disorders.

Assumed Disturbances of Circadian Rhythms

Period

Rapid cycling in bipolar affective illness was explained by Halberg[1] as a beat phenomenon due to the interaction of circadian rhythms entrained to the 24-h routine of daily life with a free-running rhythm of, for example, adrenocortical activity. The cycle length of psychopathology should then be predictable from the period of this nonentrained and the entrained (24-h) rhythm—or vice versa: The period of the free-running circadian rhythm should be predictable from the 24-h period of entrained circadian rhythms and the period of the cycles of the mental disorder.

This concept was demonstrated rather than validated on the basis of data from a single case study in a rapid cycler.[2] Later it was supported by self-assessed oral temperature data in an outpatient suffering from rapidly cycling bipolar affective illness.[3] The same authors also reported the occurrence of free-running biological rhythms in other outpatients with rapidly cycling manic-depressive disease who had taken the measurements themselves during the illness. Unfortunately, it cannot be excluded that the abnormalities were entirely caused by unreliable data due to the mental state in which the patients took the measurements.

Some light is thrown on this problem by case reports from another group of researchers. They had found a 22.5-h component in addition to the 24-h component

in the periodogram of oral temperature during an episode of a bipolar II depression when the patient was hospitalized. This component did not appear in a data set obtained by the patient herself after clinical recovery and during subsequent episodes.[4] Nevertheless, the finding was interpreted by the authors as reflecting a free-running period rather than problems in taking the measurements. Because of the lengthening of the free-running circadian period in plants and lower animals by lithium it was even inferred that the prophylactic effect of this compound in recurrent affective disorders was caused by a normalization of an abnormally fast endogenous rhythm in afflicted human subjects.[5] However, in five other depressives subsequently studied by Pflug et al.,[6] no such abnormality could be detected in the circadian rhythm of oral temperature. In our own investigation of a larger number of depressives,[7,8] no free-running period could be ascertained in the power spectrum of rectal temperature, urinary free cortisol, or any other variable.

Phase

Despite the mainly negative findings regarding free-running circadian periods in depressives living in an environment with a 24-h routine, the idea of an abnormally fast endogenous rhythm of the main circadian clock was not given up. It was argued that the clock might be reset every day by external time cues; the phase of circadian rhythms, however, would then be advanced owing to the driving force of the main circadian pacemaker that tended to go faster than in a state of mental health.[9,10] Such a phase-advance of circadian rhythms was indeed described for several variables, e.g., cortisol and core body temperature.[9,10] The early timing of the first rapid-eye-movement (REM) period during night sleep[11] was, in this context, considered as reflecting a phase-advance of the REM propensity cycle. However, subjects with early REM episodes at the beginning of night sleep also tend to have a shortened REM latency after awakenings in the middle of the night[12] or during daytime naps,[13–15] thus indicating that it is a sleep onset phenomenon unrelated to the circadian REM propensity cycle.

Furthermore, the findings of a phase-advance of biological rhythms are far from being consistent.[16–18] For example, if rectal temperature is continuously measured at night over a period of several days[19] or more[20] in depressives and control subjects of similar sex and age distribution, no difference with respect to the circadian phase position can be ascertained. With respect to the cortisol rhythm, an early timing of either the circadian maximum[21] or, more often, the circadian minimum,[22–25] but never of both the maximum and the minimum together, was described, the most consistent finding being an early timing of cortisol secretion after the evening trough.[26] Because this finding may well be related to the patients' sleep disorder[17] it is indispensable to study this relation in more depth before speculating about an underlying dysfunction of circadian clocks.

The phase-advance hypothesis has received some support from studies concerning therapeutic interventions. Thus advancing the sleep time by several hours alleviated the clinical condition in some depressives, either as the only therapeutic measure[27] or in combination with preceding partial sleep deprivation.[28] The interpretation of this effect, however, is difficult, as the sleep advance implies a sleep deprivation during the second half of the night, which in itself seems to be of therapeutic value.[29] It is therefore doubtful whether it is this effect or that of the early timing of sleep as such (or some kind of placebo effect?) that induces the clinical improvement. Other evidence for the phase-advance hypothesis is seen in the property of some antidepressants to delay the phases of circadian rhythm

in animals.[30] Investigations regarding classical antidepressants are still scarce, however, and the respective results are inconsistent.[31] Furthermore, there is no evidence of a phase delay of hormonal rhythms (melatonin as well as cortisol) during a 3-week trial with the tricyclic antidepressant desipramine in human subjects; rather, there is a trend in the opposite direction.[32]

Amplitude

The amplitude of several circadian rhythms was reported to be diminished during episodes of depression. Because this finding was found not only in the average educed waveform derived from a series of cycles but also in individual cycles of, for example, the cortisol rhythm,[33] it cannot, at least not exclusively, be explained by the intraindividual variation of the temporal location of the maxima and minima.[6] However, in carefully designed studies no change or even an increase in amplitude of the cortisol rhythm[7] was ascertained, and in core body temperature only the decrease during night sleep was found to be attenuated.[19,20] Because it may well be related to stress and sleep disturbances experienced by the patients,[16,17] it does not seem justified to draw conclusions regarding circadian clocks.

Circadian Sleep Parameters

As is well known from everyday life experience and experimental sleep research,[34] sleep propensity exhibits a circadian rhythm. Some authors[35,36] believe that it can be ascribed to the influence of the circadian pacemaker governing the rhythmicity of other circadian functions (e.g., adrenocortical activity, renal excretion of water and electrolytes, core body temperature). Others[37,38] postulated the existence of a separate internal clock for the circadian modulation of sleep propensity. Although sleep disturbances are prominent in affective disorders and early morning awakening is one of the core symptoms of melancholia.[11] dysfunctions of this hypothetical clock for the sleep-wake cycle have rarely been suggested as causing or accompanying episodes of affective disorders. An exception is the hypothesis of a lengthening of the internal period of this clock in manic episodes, particularly at the time of switch from depression to mania.[39] This fact should explain the occurrence of 48-h sleep-wake cycles at this stage of a bipolar illness. However, an alternative explanation of this phenomenon, which does not assume any change in the period of a circadian clock, is based on Borbély's[35] two-process model of sleep regulation: During a state of hyperactivity with severe hyposomnia, total sleep loss during one night is compensated for the next night, and so forth.[16]

The two-process model was also used to explain the typical sleep pattern in depressives.[40] It was suggested that a deficiency of a hypothetical sleep factor caused early morning awakening, as the low amount of this factor accumulated until the beginning of night sleep was inactivated much earlier than a normal amount. This finding leads to the prediction of a lengthening of the sleep-wake cycle under free-running conditions.

Findings in Patients Isolated from External Time Cues

Subjects

Up to now, observations of circadian rhythms in five affectively ill patients investigated in an environment without external time cues have been published: One was a 66-year-old man studied by our group in Munich[41–43]; the four others,

all of them women within the age range 36–56 years, were studied by Wehr et al.[44] at the U.S. National Institute of Mental Health (NIMH). The five patients cover a wide range of affective psychopathologies and courses. With the exception of case 5, they were free of drugs before and during the investigation. Two were unipolar depressives; one of them (our case 1) exhibited regular 48-h cycles of the disorder for 12 years, and the other (case 2) suffered from a typical episode of unipolar major depression. Of the three bipolar patients, one (case 3) had developed rapid cycling with an average cycle length of 6 days, one (case 4) was suffering from a typical bipolar manic-depressive psychosis, being in a depressive episode when the experiment started; the last one (case 5) had been hypomanic for several weeks after antidepressive medication with a selective type A monoamine oxidase inhibitor (MAOI), which she continued to take during the study. (It should be noted that, due to the inclusion of our Munich patient, the number of patients studied at the NIMH has increased by one compared with those in the study by Wehr et al.[44])

Predictions

From the above-mentioned hypotheses the following predictions for these subjects during temporal isolation can be inferred.

1. If the basis of 48-h rhythms of depression is an interaction of a free-running rhythm (with a period length of 16 h) with the entrained 24-h rhythm, the first subject studied should either exhibit a 16-h component in one circadian rhythm that might have been obscured in a 24-h regimen or he should switch to a 16-h period with all his rhythms.[43] In the latter case, the depression should disappear, as there would no longer occur a state of internal desynchronization of biological rhythms assumed to be at the origin of rapid cycling.
2. If the internal clock had a tendency toward a shorter than 24-h period, this tendency should become obvious in the nonentrained state. If a deficiency of a sleep factor was present, however, the sleep-wake cycle should free-run with an abnormally long period, i.e., much longer than the usual 24-h period in the state of free-run.[37] It should also alleviate the sleep disturbances of this patient including the early occurrence of REM episodes.
3. If Halberg's hypothesis[1] were valid for this case of rapid cycling, a period of 20 or 28 h should become apparent in the nonentrained state; and if no other period occurred, the cycles of psychopathology should be abolished—analogous to the predictions for case 1.
4. As long as he is depressed, this patient should display a shortening of circadian rhythms (similar to case 2). In case of a switch to mania, this shortening should be reversed, at least with respect to the sleep-wake cycle, which then should adopt a period much longer than 25 h, probably around 50 h.
5. Except for a possible lengthening of the sleep-wake cycle, no definite conclusions for this hypomanic patient can be drawn. In fact, according to the literature, the slightest deviation from a normal synchronized 25-h rhythm would be expected in comparison to patients in a depressed state.

Results

In none of the five data sets were these predictions fulfilled. On the contrary, the findings were not only negative in this respect but pointed to other directions.

1. The 48-h cycles of depression persisted, and internal desynchronization occurred with irregular sleep-wake cycles varying around 19 h, whereas the biological variables such as rectal temperature, renal excretion of water, electrolytes, and free cortisol exhibited a more regular, nearly 24-h rhythm.
2. Despite only slight improvement of the depression, the circadian sleep-wake and temperature rhythms lengthened slightly to an average of around 24.5 h with a normal proportion of sleep and wakefulness (around 1:2) and the REM latency remaining short (47 min instead of 50 min in the entrained state).
3. The sleep-wake and temperature rhythms lengthened in a normal fashion to an average of 25 h per cycle with a normal percentage of sleep. No evidence of a 20- or 28-h component appeared in the sleep-wake or temperature rhythms. Nevertheless, the cycling of psychopathology persisted without any perceivable change in its temporal pattern.
4. During the experiment, a switch from depression to mania occurred. It was temporally associated with a reduction in the initially slightly increased cycle length. Because of a large scatter of the times awake or asleep during each cycle in combination with a general tendency to short sleep periods, the pattern became rather irregular.
5. Unexpectedly, a seriously disturbed circadian sleep-wake pattern and a comparable disruption of the temperature rhythm appeared in this hypomanic patient. The authors interpreted their findings as indicating repeated changes in the period of the sleep-wake rhythm and its desynchronization from the temperature rhythm. Close inspection of the data, however, reveals concordant changes in the sleep-wake and the temperature rhythms as well as irregular fluctuations of both of them around a 24-h period rather than any systematic changes in the underlying periods. As under entrained conditions, the average sleep time of this patient was remarkably short, averaging less than 20% per cycle with a broad range of variation.

Conclusions

None of the aforementioned chronobiological hypotheses of affective disorders could be substantiated by findings obtained in an environment without zeitgebers. Remarkably, in only one of the five subjects (case 1) did internal desynchronization between the sleep-wake and the temperature rhythms seem to have occurred. This subject was a rapid cycler displaying 48-h cycles of unipolar depression that persisted in isolation from external time cues. The predicted 16-h component of a free-running rhythm was not observed in his shortened sleep-wake cycle, which varied markedly around 19 h, or in any of his vegetative rhythms, which remained near 24 h. In the other rapid cycler (case 3), the sleep-wake and the temperature rhythms remained synchronized, the periods lengthening to slightly more than 24 h. This finding is well in line with findings in healthy subjects. Similarly, in one typical case of unipolar depression (case 2), no deviation of the endogenous circadian rhythm could be revealed in temporal isolation. The period became longer, not shorter, as predicted by the phase-advance hypothesis. On the other hand, the period of the sleep-wake cycle did not increase beyond the average free-running period of healthy subjects, a finding that contradicts the sleep factor deficiency hypothesis.

In a bipolar manic-depressive (case 4), the period of the sleep-wake cycle showed a tendency toward shortening when the patient switched from depression to mania, not the other way round. This finding is exactly the opposite of what was expected

from the interpretation of alternating nights of sleep and sleeplessness during such switches in an entrained environment indicating a lengthening of the endogenous period of the sleep-wake cycle. However, the tendency toward hyposomnia increased in the manic state, which is concordant with the assumption that the abnormal sleep pattern during switches from depression to mania can be explained as an expression of severe hyposomnia in an otherwise undisturbed circadian system.

Finally, a severe disruption of circadian rhythms was observed during a rather stable state of hypomania, a finding that could not be predicted from any of the current chronobiological hypotheses on affective disorders outlined above.

These hypotheses should no longer serve as guidelines for chronobiological investigations in affective disorders. Rather, they should be substituted by new theoretical approaches to the circadian phenomena in these disorders. Suggestions have been made in previous reports from our group.[16–18,42,45] The available space does not allow their detailed description. They have in common that mechanisms such as masking of biological rhythms by the disease process in the brain, and vice versa, and an entrainment of this process to signals from the circadian system are at work. Findings for or against these theoretical assumptions must be obtained by further investigations of patients, control subjects, and animal models.

References

1. Halberg F. Physiologic considerations underlying rhythmometry with special reference to emotional illness. In Ajuriaguerra J de (ed): Cycles Biologique et Psychiatrie. Paris: Masson, 1968; 73–126.
2. Bryson RW, Martin DF. 17-Ketosteroid excretion in a case of manic-depressive psychosis. Lancet 1954;2:365–367.
3. Kripke DF, Mullaney DJ, Atkinson M, et al. Circadian rhythm disorders in manic-depressives. Biol Psychiatry 1978;13:335–351.
4. Pflug B, Erikson R, Johnsson A. Depression and daily temperature: a long-term study. Acta Psychiatr Scand 1976;54:254–266.
5. Engelmann W, Pflug B. Rhythmische Aspekte der Lithiumwirkung. In Heimann H, Pflug B (eds): Rhythmusprobleme in der Psychiatrie. Stuttgart: Fischer, 1978;65–74.
6. Pflug B, Johnsson A, Martin W. Alterations in the circadian temperature rhythms in depressed patients. In Wehr TA, Goodwin FK (eds): Circadian Rhythms in Psychiatry. Pacific Grove: Boxwood Press, 1983;71–76.
7. Von Zerssen D, Barthelmes H, Dirlich G, et al. Circadian rhythms in endogenous depression. Psychiatry Res 1985;16:51–63.
8. Dirlich G, Barthelmes H, von Lindern L, et al. A chronobiologic study of depression: discussion from a methodologic perspective. In Halaris A (ed): Chronobiology and Psychiatric Disorders. New York: Elsevier, 1987;133–158.
9. Wehr TA, Goodwin FK. Biological rhythms and psychiatry. In Arieti S, Brodie HKH (eds): American Handbook of Psychiatry, Vol. 7: Advances and New Directions. 2nd Ed. New York: Basic Books, 1981;46–74.
10. Wehr TA, Goodwin FK. Biological rhythms in manic-depressive illness. In Wehr TA, Goodwin FK (eds): Circadian Rhythms in Psychiatry. Pacific Grove: Boxwood Press, 1983;129–184.
11. Gillin JC, Sitaram N, Wehr T, et al. Sleep and affective illness. In Post RM, Ballenger JC (eds): Neurobiology of Mood Disorders. Baltimore: Williams & Wilkins, 1984;157–189.
12. Schulz H, Tetzlaff W. Distribution of REM latencies after sleep interruption in depressive patients and control subjects. Biol Psychiatry 1982;17:1367–1376.
13. Kupfer DJ, Gillin JC, Coble PA, et al. REM sleep, naps and depression. Psychiatry Res 1981;5:195–203.
14. Pugnetti L, Colombo A, Cazzullo CL, et al. Daytime sleep patterns of primary depressives: a morning nap study. Psychiatry Res 1982;7:287–298.

15. Elsenga S, Wiegand M, Lauer C, et al. Nocturnal sleep and napping after total sleep deprivation in depression. in prep.
16. Von Zerssen D. Chronobiology of depression. In Angst J (ed): The Origins of Depression: Current Concepts and Approaches. Berlin: Springer, 1983;253–271.
17. Von Zerssen D. What is wrong with circadian clocks in depression? In Halaris A (ed): Chronobiology and Psychiatric Disorders. New York: Elsevier, 1987;159–179.
18. Von Zerssen D, Doerr P, Emrich HM, et al. Diurnal variation of mood and the cortisol rhythm in depression and normal states of mind. Eur Arch Psychiatry Neurol Sci 1987;237:36–45.
19. Avery DH, Wildschiødtz G., Rafaelsen OJ. Nocturnal temperature in affective disorder. J Affective Disord 1982;4:61–71.
20. Lund R, Kammerloher A, Dirlich G. Body temperature in endogenously depressed patients during depression and remission. In Wehr TA, Goodwin FK (eds): Circadian Rhythms in Psychiatry. Pacific Grove: Boxwood Press, 1983;77–88.
21. Dietzel M, Saletu B, Lesch OM, et al. Light treatment in depressive illness: polysomnographic, psychometric and neuroendocrinological findings. Eur Neurol 1986;25(suppl 2):93–103.
22. Yamaguchi N, Maeda K, Kuromaru S. The effects of sleep deprivation on the circadian rhythm of plasma cortisol levels in depressive patients. Folia Psychiatr Neurol Jpn 1978;32:479–487.
23. Jarrett DB, Coble PA, Kupfer DJ. Reduced cortisol latency in depressive illness. Arch Gen Psychiatry 1983;40:506–511.
24. Linkowski P, Mendlewicz J, Leclercq R, et al. The 24-hour profile of adrenocorticotropin and cortisol in major depressive illness. J Clin Endocrinol 1985;61:429–439.
25. Sherman BM, Pfohl B. Rhythm-related changes in pituitary-adrenal function in depression. J Affective Disord 1985;9:55–61.
26. Halbreich U. The circadian rhythm of cortisol and MHPG in depressives and normals. In Halaris A (ed): Chronobiology and Psychiatric Disorders. New York: Elsevier, 1987;49–73.
27. Wehr TA, Wirz-Justice A, Goodwin FK, et al. Phase advance of the circadian sleep-wake cycle as an antidepressant. Science 1979; 206:710–713.
28. Souêtre E, Salvati E, Pringuey D, et al. Antidepressant effects of the sleep/wake cycle phase advance: preliminary report. J Affective Disord 1987;12:41–46.
29. Schilgen B, Tölle R. Partial sleep deprivation as therapy for depression. Arch Gen Psychiatry 1980;37:267–271.
30. Wehr TA, Wirz-Justice A. Circadian rhythm mechanisms in affective illness and in antidepressant drug action. Pharmacopsychiatry 1982;15:31–39.
31. Wirz-Justice A. Light and dark as a "drug." Prog Drug Res 1987;31:383–425.
32. Thompson C, Mezey G, Corn T, et al. The effect of desipramine upon melatonin and cortisol secretion in depressed and normal subjects. Br J Psychiatry 1985;147:389–393.
33. Sachar EJ, Hellman L, Roffwarg HP, et al. Disrupted 24-hour patterns of cortisol secretion in psychotic depression. Arch Gen Psychiatry 1973;28:19–24.
34. Horne J. Why We Sleep: The Functions of Sleep in Humans and Other Mammals. Oxford: Oxford University Press, 1988.
35. Borbély AA. A two process model of sleep regulation. Hum Neurobiol 1982;1:195–204.
36. Daan S, Beersma D. Circadian gating of human sleep-wake cycles. In Moore-Ede MC, Czeisler CA (eds): Mathematical Models of the Circadian Sleep-Wake Cycle. New York: Raven Press, 1984;129–158.
37. Wever RA. The Circadian System of Man. New York: Springer, 1979.
38. Kronauer RE, Czeisler CA, Pilato SF, et al. Mathematical model of the human circadian system with two interacting oscillators. Am J Physiol 1982;242:R3–R17.
39. Wehr TA, Goodwin FK, Wirz-Justice A, et al. 48-Hour sleep-wake cycles in manic-depressive illness: naturalistic observations and sleep deprivation experiments. Arch Gen Psychiatry 1982;39:559–565.
40. Borbély AA, Wirz-Justice A. Sleep, sleep deprivation and depression. Hum Neurobiol 1982;1:205–210.
41. Doerr P, Von Zerssen D, Fischler M, et al. Relationship between mood changes and adrenal cortical activity in a patient with 48-hour unipolar-depressive cycles. J Affective Disord 1979;1:93–104.

42. Dirlich G, Kammerloher A, Schulz H, et al. Temporal coordination of rest-activity cycle, body temperature, urinary free cortisol, and mood in a patient with 48-hour unipolar-depressive cycles in clinical and time-cue-free environments. Biol Psychiatry 1981;16:163–179.
43. Von Zerssen D, Dirlich G, Fischler M. Influence of an abnormal time routine and therapeutic measures on 48-hour cycles of affective disorders: chronobiological considerations. In Wehr TA, Goodwin FK (eds): Circadian Rhythms in Psychiatry. Pacific Grove: Boxwood Press, 1983;109–127.
44. Wehr TA, Sack DA, Duncan WC, et al. Sleep and circadian rhythms in affective patients isolated from external time cues. Psychiatry Res 1985;15:327–339.
45. Campbell SS, Zulley J. Induction of depressive-like sleep patterns in normal subjects. In Halaris A (ed): Chronobiology and Psychiatric Disorders. New York: Elsevier, 1987;177–132.