Chronobiology and mood disorders: background and introduction

Benjamin Rusak, PhD

Departments of Psychiatry, Psychology and Pharmacology, Dalhousie University, and Chronobiology and Sleep Program, Queen Elizabeth II Health Sciences Centre, Halifax, NS

The papers in this special section are the proceedings of a symposium on chronobiology and mood disorders presented at the June 1999 meeting of the Canadian College of Neuropsychopharmacology in Halifax, Nova Scotia. These papers review aspects of mood disorders that are linked to biological rhythms with 3 different periodicities: daily, menstrual and annual. They also reflect a growing interest in mechanisms regulating physiological rhythmicity on a variety of time scales and in the impact of normal and pathologic function of these mechanisms on psychiatric illnesses.

Rhythms are related to mood disorders in several different ways. First, some conditions are expressed cyclically; that is, they have a period linked to an identified internal or external periodicity, such as menstrual and annual rhythms of dysphoria or depression. Other conditions, such as many cases of bipolar illness, express cycles that are not tied to any identified periodic stimulus. A second connection between rhythms and mood disorders is the alteration of daily rhythms, in particular sleep and waking, in mood disorders. Finally, the systems responsible for the generation or synchronization of normal rhythms may be involved in the etiology of mood disorders, as has sometimes been proposed, for example, for bipolar illness and for seasonal affective disorders.

Connections between psychiatric disorders and biological rhythms were reviewed more than 40 years ago in a landmark monograph by Curt Paul Richter, whose innovative concepts and studies gave birth to many fields of psychobiological research, as well as establishing key concepts and analytic methods for the study of biological rhythms. Richter's 1965 monograph *Biological Clocks in Medicine and Psychiatry*[1] presented material from two 1959 Salmon Lectures to the New York Academy of Medicine. It serves as a benchmark for assessing the developments in this area of research over the last few decades.

C.P. Richter and rhythms in human physiology

In these lectures, Richter reviewed several decades of observations of periodicity in physiological and behavioural functions in his animal laboratory and at the Phipps Psychiatric Clinic of Johns Hopkins Hospital. His review summarized evidence of cyclic phenomena in a wide range of clinical symptoms, both medical and psychiatric, in humans, and in the behaviour and physiology of several rodent species.

Richter had devoted many years to a detailed analysis of the activity patterns of rats and had demonstrated the persistence, in constant environmental conditions, of an internally generated near-24-hour rhythm that could be synchronized to environmental 24-hour lighting cycles. He also described a variety of shorter- and longer-period rhythms in rodents, and a few in humans. He was, however, unimpressed with the

Correspondence to: Dr. Benjamin Rusak, Queen Elizabeth II Health Sciences Centre, 9214 Lane Building, 5909 Veterans' Memorial Lane, Halifax NS B3H 2E2; fax 902 473-4596; rusak@is.dal.ca

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cyclicity of physiology and behaviour in normal humans. He identified a 90- to 120-minute cycle of gastrointestinal activity (studied by Tomi Wada in his laboratory); a 24-hour periodicity; the 28-day menstrual cycle; and the 280-day periodicity of pregnancy. But he stressed that the 24-hour periodicity that formed the core of his observations in rodents was poorly expressed in normal humans, and that evidence for its existence was "not very definite."

Richter recognized that healthy humans showed small changes in body temperature and other functions during the day, but lack of control of human environments made it difficult to determine what caused these changes. He speculated that causes might include daily sleep, work or eating habits, or internal cues such as the rhythm of gastrointestinal activity. The main evidence supporting the existence of a 24-hour human clock, according to Richter, was "reported discomfort experienced by air travelers who lose or gain six to seven hours in a few hours' travel time." He reported, however, that this new phenomenon (now called jet lag) was not consistent, and he was not convinced by this evidence.

In fact, he wrote that, in order to demonstrate such a clock in humans, "it will be necessary to take records of various functions of individuals maintained under rigidly controlled constant conditions, in bed, for several twenty-four-hour periods. To my knowledge, no such records exist at the present time." Richter was apparently unaware of attempts to address this question in the late 1950s in the laboratory of Jürgen Aschoff and colleagues in Bavaria.[2] Even those studies conducted in temporal isolation in underground bunkers did not meet the strict criteria Richter imposed, which included both continuous bed-rest and starvation for 3 or 4 days.

Rhythms in pathologic conditions

Richter recognized the daily light–dark cycle as the dominant time cue in the lives of other species, but speculated that humans had gradually become emancipated from regulation by their 24-hour clocks because of their control of exposure to light, at first firelight and then other artificial light sources. Nevertheless, he devoted much of his monograph to the description of a wide range of periodic symptoms and illnesses in humans. Based on both his own observations and numerous publications by others, he described rhythms in symptoms in a variety of conditions, including mania and depression, peptic ulcers, Parkinson's disease, epilepsy and schizophrenia. The rhythmic features included the primary symptoms of each illness as well as measures such as nitrogen excretion, white blood cell counts and body temperature. The expressed periodicities ranged from 12 hours to 10 years, and Richter relied particularly on the detailed observations of Kraepelin on long-period cycles of depression and mania.

Some of the cycles that Richter described had periods that are easily related to major periodicities in the environment, such as 24-hour or annual cycles in depressive symptoms or in mania. Other cycles, however, had periods of 30, 40 or 52 days, 15 months, 2 or 10 years. These are not obviously tied to any known aspects of environmental rhythmicity, nor to any known features of normal physiology. Richter developed an hypothesis, which he called the "shock-phase hypothesis" to account for these cycles. According to this hypothesis, each component (typically a cell) in any organ or brain structure functions with an inherent periodicity. This periodicity may be different for each cell type, and individual cells may normally be synchronous in their activity, giving rise to a characteristic functional rhythm in each organ.

According to the hypothesis, in the course of evolution this primitive cellular synchrony gives way, especially in humans, to functional asynchrony among constituent cells in an organ. The benefit of this lack of synchrony is presumed to be that the performance of organs and structures overall becomes more consistent over time, which is useful for humans who have presumably been emancipated from the need to express strong (e.g., daily) rhythms. "Over the course of thousands of years, manifestations of man's clock have gradually become less and less profound, his survival depending more and more on smooth even performance around the twenty-four hours of the day."

Exposure to an acute stressor or trauma, however, may serve to synchronize the out-of-phase cells and result in synchronous output, with a periodicity characteristic of the particular cell type involved. This periodicity might then be maintained, leading to persistent rhythmicity in symptoms, such as swelling in joints or acute attacks of mania. Alternatively, the shock-imposed synchrony might gradual dissipate, or might be disrupted by medical or other interventions that restore a more healthful desynchrony among cells.

Rhythmicity in normal humans

Richter emphasized the clear presence of endogenous rhythms in normal, healthy rodents, their virtual absence in normal, healthy humans, and their emergence in humans under conditions of stress or illness. The conclusion that rhythms, especially daily rhythms, do not characterize much of normal human physiology contrasts to the view that has emerged over the last 40 years. A wealth of studies using methods at least partially satisfying Richter's strict criteria have documented daily (circadian) rhythms in humans, generated internally and synchronized by external cues, in particular, lighting cues, as Richter had documented in other mammals.[2,3] Daily (and annual[4]) rhythms in human physiology and behaviour are now recognized as pervasive.

In addition, the rhythmicity of our physiology on many time scales is now recognized as important to normal function, rather than a property of pathologic conditions. The need for pulsatile release of hypothalamic-releasing hormones to maintain normal responsiveness of pituitary tissue is a classic example of a high-frequency rhythm with a critical and well-characterized physiological function.[5] Thus, in contrast to Richter's argument, it is now widely accepted that rhythmicity is an important part of normal human physiology. The emphasis that Richter placed on rhythmicity in medical and psychiatric conditions has, however, also been strongly reinforced. As reviewed in the accompanying papers, specific forms of psychopathology have been linked to changes in daily rhythms and sleep–wake cycles, to menstrual rhythmicity and to annual cycles. What has changed is our view of how these cycles of symptom expression arise: these are now typically linked to perturbations of the mechanisms underlying normal rhythmicity.

This analysis suggests that the shock-phase hypothesis is not needed to explain human psychopathology-linked rhythms that have periods similar to those of normal human physiology (e.g., daily, menstrual, annual). The mechanisms giving rise to cyclic illnesses with very different periods remain unknown. Despite the lack of scientific interest in the shock-phase hypothesis for many years, an intriguing recent study lends some general support to the idea. A study of cultured rat fibrolasts demonstrated the emergence of several circadian cycles of gene expression in response to a single (hence, aperiodic) shock of high-concentration serum delivered to the culture system.[6] This observation suggests that even cells that appear to have no inherent rhythmicity may begin to express rhythms in response to a single external perturbation. It is possible that the external stimulus acted to synchronize rhythmic but asynchronous cells, or to initiate rhythms in cells with an unexpressed potential for circadian rhythmicity. Thus, regardless of the validity of Richter's model for explaining longer-period rhythms in human pathology, this observation supports the idea that rhythmic mechanisms may lie latent in a variety of somatic and neural tissues, and that rhythmicity may emerge in response to a perturbation.

Symposium papers

The following review papers discuss the connections between rhythms and human psychopathology expressed on different time scales. These rhythms appear to result from disruptions of mechanisms that regulate normal rhythms in human physiology or from exaggerations of their normal effects. The exact mechanisms that link sleep, circadian rhythms, endocrine cycles and photoperiod changes to mood disorders remain, however, matters of active debate and research. These reviews describe the extent of our current knowledge of the mechanisms involved, clinical applications of this knowledge, and directions in which future research on these topics might proceed.

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