Chapter

Introductory Chapter: Chronobiology - The Science of Biological Time Structure

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1. Introduction

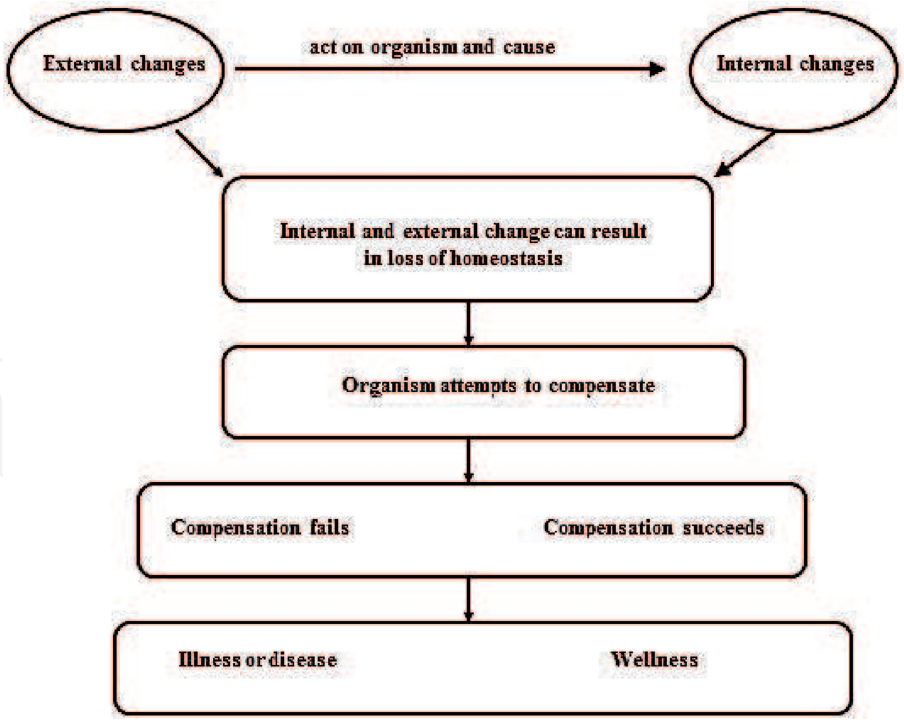
Both humans and most animal species on our planet are exposed to regular alternations of light and darkness, with a constant periodicity of 24 h throughout their lifetime. This regular alternation of light and dark affects not only human biological systems but also the social organization of behavior. Processes occurring in the human organism, which are dependent on the periodic alteration and alternation of environmental factors, potentially affect the blind and those employed in shift work and "nocturnal types," whose habits deviate from the usual mode of most individuals. The mode of alternating light and darkness is different at the equator, behind the polar circles, and also at transitions across multiple time zones. The effect of such light modes is manifested in periodic changes in several physiological functions and biological rhythms exhibited at every level of life—in single cells, tissues, organs, and, ultimately, physiological systems of organisms.

Changes in the external environment, such as those of the weather or atmospheric conditions, can be **unpredictable**; therefore, organisms need systems that directly respond to changing environments. However, there are also **predictable** changes, which are the result of specific planetary movements such as the day-night cycle (rotation of the earth on its axis), the cycle of the moon (cycle of the moon around the earth), or annual cycles (cycle of the earth around the sun). For these predicable changes, organisms have specific mechanisms that generate endogenous biological rhythms corresponding directly to certain periodicities in the environment. They are not directly dependent on the rhythmicities of environment but only use the periodic information from the environment to synchronize biological oscillations with cycles of environment.

2. Biological rhythms and homeostasis

Biological rhythms are sequences of events that are repeated over time in the same manner and with the same interval; in other words, they are predictable in time. Biorhythms of organisms are the result of adaptation to changes in the environment, which is highly variable and exhibits variation in many factors. Chronobiology is the science investigating and objectively quantifying the mechanisms of biological time structure, including the rhythmic manifestations of life.

Because medicine is, in large part, based on homeostatic principles, the following scheme may be regarded as representative.



The survival of the animal in a highly periodic "day-night" environment, therefore, depends on the approximate timing of its reactions. Physiological systems must integrate and subsequently influence the responses of each system to different times of the day. Therefore, the traditional concept of homeostasis began to change. The **old concept of homeostasis** states that physiological variables are relatively constant only in a narrow physiological range throughout the day, which is essential for health. All organs and tissues of the body perform functions to maintain these constant conditions. However, the traditional concept of homeostasis involves no time dependence on the following:

- Results of diagnostic tests
- Occurrence or worsening of disease manifestations
- Pharmacokinetics of drugs
- Sensitivity to drugs
- Sensitivity to drugs in terms of pharmacodynamic—either therapeutic or side effect—drug properties

In contrast, the new concept of homeostasis states that physiological variables oscillate and are adjusted only to a narrow physiological range throughout the day, which is essential for health, and all organs and tissues of the body perform functions to maintain these constant conditions.

3. Distribution of biological rhythms

Exogenous rhythms: exogenous rhythms are oscillations of the passive system that depend on periodic stimulus from the external environment to which the organism synchronizes with these rhythmical changes. They are only observed within the circadian periodicity of the social or climatic environment.

Endogenous rhythms: endogenous rhythms are independently oscillating systems that are able to maintain their periodicity and also under constant nonperiodic conditions. Endogenous rhythms include:

Circadian rhythms: oscillate with a period of approximately 24 ± 4 h. They are one of the most frequently followed and studied rhythms. The term "circadian" was first used by professor [1] and has essentially two meanings. The first describes the day and night part of the day as a whole and the second as a cycle with a period of approximately 24 h.

Ultradian rhythms: oscillate with a period <20 h. The frequency of ultradian rhythms varies considerably from one species to another and from one parameter to another. In humans, several functions oscillate in 60–120 min intervals, and these rhythms are sometimes superimposed on other functions that oscillate at 3–5 min intervals.

Infradian rhythms: oscillate with the period >28 h. This term includes:

- *Circaseptan rhythms*: oscillate with a period of approximately 7 ± 3 days.
- *Circalunar rhythms*: rhythms with a period about 30 ± 5 days. Includes ovarial activity and the menstrual cycle in adult women.
- *Circannual rhythms*: oscillate with a period of approximately 1 year (±2 months), synchronized or desynchronized within a calendar year. It also includes *seasonal rhythms* that are the result of an adaptation process of living organisms to the environment. In certain species, reproductive functions are stimulated at specific moments in the annual cycle, thus optimizing the survival of the species. Although seasonal rhythms are also observed in humans, they do not exist to support species preservation.

4. Control of biological rhythms

The control of circadian rhythms occurs at the level of the retina (light input), the suprachiasmatic nuclei of the hypothalamus (clock genes), and the pineal gland (melatonin synthesis). Daylight or equivalent simulated light impacts retinal cells and passes the retinohypothalamic tract into the hypothalamic suprachiasmatic nuclei, which are referred to as the "internal clock." The current hypothesis regarding the multioscillatory structure of the circadian system [2] contains the following components [3]:

Inputs: environmental periodic cues can reset the phase of the central pacemaker so that the period and phase of circadian rhythms become coincident with the timing of external cues.

Central pacemakers: the suprachiasmatic nucleus or nuclei (SCN) is considered to be the major pacemaker of the circadian system, driving circadian rhythmicity in other brain areas and peripheral tissues by sending them neural and humoral signals.

Peripheral oscillators: most peripheral tissues and organs contain circadian oscillators. Usually they are under the control of the SCN; however, under some circumstances (e.g., restricted feeding, jet lag, and shift work), they can desynchronize from the SCN.

Outputs: central pacemakers and peripheral oscillators are responsible for the daily rhythmicity observed in most physiological and behavioral functions. Some of these over-rhythms (physical exercise, core temperature, sleep-wake cycle, and feeding time), in turn, provide feedback, which can modify the function of the SCN and peripheral oscillators.

5. Chronobiological terminology

The terminology accepted and approved in the field of chronobiology by The American Association of Medical Chronobiology and Chronotherapeutics describes aspects of biological rhythms that are often used in chronobiological texts, and for which no alternative terminology is suitable. This nomenclature was presented at the fourth Postgraduate Course of Medical Chronobiology and its Applications, held in Nevşehir [4]. As with other medical disciplines, the following terms must be introduced and should be accepted by specialists in this field. However, chronobiology is a rapidly evolving discipline, and, moreover, many of the established terms in the field of chronobiology remain unknown to many scientists and physicians who can benefit from applying chronobiological principles to their work.

Biological clocks: self-sustained oscillators that generate biological rhythms in the absence of external periodic input (e.g., at the gene level in cells).

Pacemaker: the functional unit capable of self-sustaining oscillations, which synchronize other rhythms or internal mechanisms, which sets the period and phase of the endogenous rhythm. They are oscillators (biological o'clock), which generate biological rhythms in the absence of external periodic inputs (e.g., at the gene level in individual cells). The hypothalamic suprachiasmatic nuclei are the dominant pacemaker of many circadian rhythms in mammals.

Synchronization: the state of a system when two or more variables exhibit periodicity with the same frequency, acrophase, and phasic relation. It refers to the adjustment of endogenous rhythm to external periodic influences. This influence is mediated by the synchronizer (**zeitgeber**)—the environmental periodicity determining the temporal placement of a biological rhythm along an appropriate time scale.

Human synchronizers can be:

- knowledge of the time of day
- light-dark cycle
- social contacts
- sleep-wake cycle
- time of eating
- electromagnetic field, gravitational field, and cosmic radiation

Desynchronization (internal): a state in which two or more previously synchronized variables within the same organism (endogenous rhythms) cease to exhibit different time relations.

Desynchronization (external): desynchronization of biological (endogenous) rhythm from an environmental cycle.

Free-running rhythms: endogenous rhythms with their own periods, which also persist under conditions in which the periodicity of the external environment is modified or eliminated.

Phase shifts: if the period or timing of a dominant synchronizer changes, endogenous circadian rhythms, but synchronized with environment, follow a shift of their synchronizer and display phase advances or phase delays. The rhythms adapt to this new condition in a time—re-entrainment.

Phase advance and phase delay: involves the earlier or later occurrence of a rhythm's phase, usually acrophase.

Entrainment: coupling of two rhythms of the same frequency to one of them (the entraining agent or synchronizer) determining the phase of the other. It is coupling of endogenous rhythms to an environmental oscillator of the same frequency or determination of the phase of biological rhythms by an internal pacemaker.

Self-sustained oscillation: a system that can make use of a constant source of energy and is able to continue to oscillate without outside energy input.

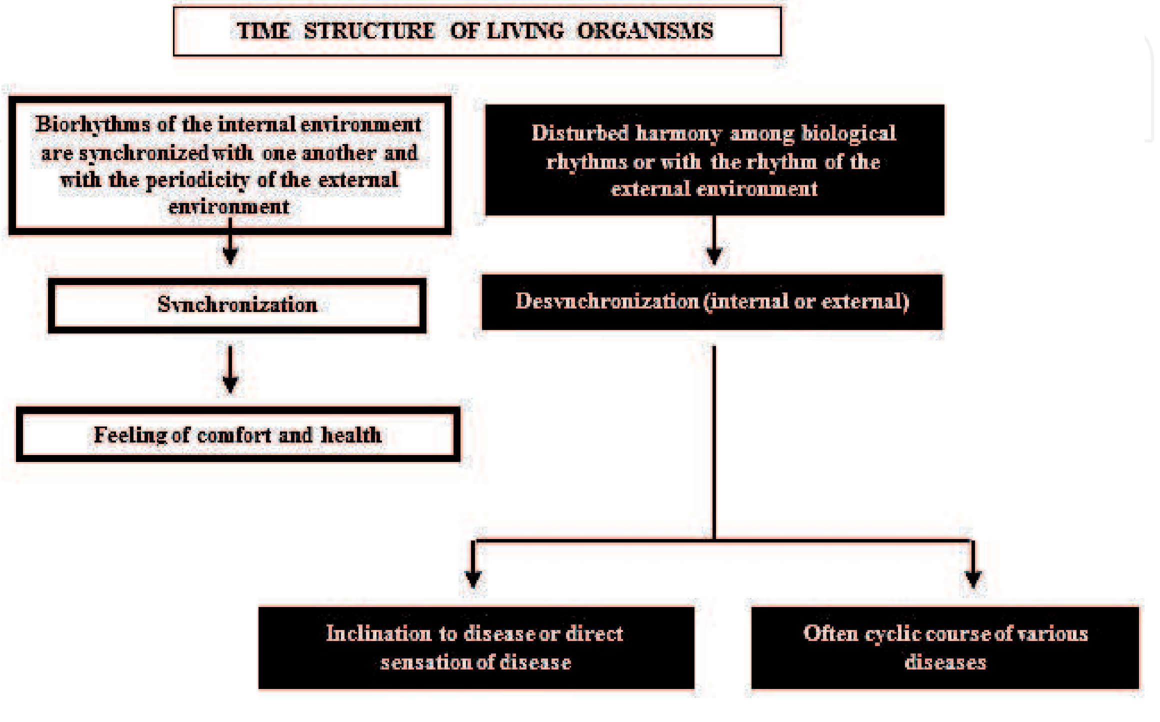
Episodic variation: apparently irregular (nonrhythmic) variation of a biological variable (e.g., episodic secretion of certain hormones).

Reference rhythm and marker rhythm: is the rhythm of one variable used as a time reference for other rhythms.

6. Clinical medicine: chronomedicine

After the discovery of the mechanism of circadian rhythm, functioning did not last long, and numerous studies were carried out describing their impact on the etiopathogenesis of diseases as well as the possibility of their application in therapy. Even in the 3–6 weeks after birth, the internal clocks are gradually synchronized with 24-h period. In the greatest extent, the influence of lighting shares on this synchronization, but the role of melatonin, which is found in breast milk only at night, is also discussed. However, circadian rhythms also occur in the blind people, and even 50–75% blind people indicate that they suffer by sleep disorders.

Periodic phenomena are encountered in many studies investigating various diseases. Very often, many symptoms or significant remissions exhibit a cyclic course. The time structure of living organisms is the source of these phenomena: accurate intermodulation over time, changing biological variables, and similar. If the harmony between and among biological rhythms is disrupted or disordered, the subjects themselves detect susceptibility to the disease or the disease itself. It is necessary to capture these different situations by monitoring the biological phenomenon during the day and to estimate the periodicity of the system using precise statistical methods.



The question, then, is when to perform laboratory examinations or diagnostic tests. For example, plasma cortisol exhibits a circadian rhythm. Although secretion increases in response to the stressful stimulus, it is spontaneously released during the day with peak values around 4:00–6:00 in the morning, with a gradual decrease during the day to the lowest values that fall between 23:00 and 2:00 a.m. If the value of "normal" occurs at approximately 08:00 h, approximately 20:00 h would represent Cushing syndrome. If the value of "normal" occurs at approximately 20:00, 08:00 h would represent Addison disease. From a circadian perspective, the conclusion is adrenal cortex hyperactivity would be diagnosed only if a high plasma cortisol concentration was found in the evening and adrenal cortex insufficiency if low levels were found in the morning.

What can be a recommendation? Creation of "individual chronobiological profile" to use of improvement of the diagnostic test accuracy problems at which is not possible to suppose that internal circadian time is equal to the real time:

- At the transitions through more time zones (jetlag syndrome)
- In shift workers
- In students during examination periods
- During hospitalization—at the relative constant levels of murmurs, light, and at the continual work of nurse
- Resulting in the disorders of the circadian orientation, although the normal phase orientation is at the start

7. Circadian disruption: disruption of biological timing

The circadian system optimizes daytime behavior and physiology and is organized hierarchically with central clocks in the SCN that are primarily synchronized by light. Currently, we are commonly exposed to less light and more night-light due to artificial lighting, which can negatively impact the organization of the circadian system and disturb sleep, resulting in extensive adverse effects on metabolic health. Interrupted sleep, for example, supports the increase of energy intake and reduction of energy expenditure, which may affect healthy eating. Experiments have also demonstrated that circadian deviations can lead to several metabolic abnormalities [5].

Circadian rhythm disturbance may occur from the level of the molecular clock (which regulates cellular activity) to the mismatch between behavioral and environmental cycles [5]. It is the result of a phase shift in the oscillation of the circadian and activity-controlled physiological processes. A recent study found that chronic disruption of one of the most basic circadian (daily) rhythms—the day-night cycle—leads to weight gain, impulsivity, slower thinking, and other physiological and behavioral changes in mice, similar to those observed in individuals who engage in shift work or experience jet lag.

This circadian pathology can be induced by factors related to **inputs** such as low contrast between day and night synchronizing signals (continuous light, frequent snacking, low levels of physical exercise), by zeitgebers with different periods or unusual phasing (i.e., light at night, nocturnal eating, nocturnal physical activity), or by zeitgeber shifts (i.e., daylight saving time, crossing time zones, shift work).

Shift work: because individuals in various occupations often work at night, they are exposed to an extraordinary risk for circadian rhythm and sleep disturbances [6–9].

Shift workers are also susceptible to other health disorders such as gastrointestinal problems [10], and exposure to work-related changes can be associated with the risk for certain diseases, including breast cancer and metabolic syndrome [11, 12].

Jetlag: in addition to shift work, jetlag also induces circadian rhythm and sleep disturbances. Although the health consequences of frequent jetlag are ambiguous [13], any harmful effects of jetlag-induced circadian rhythm and sleep disturbances are becoming more widespread as an increasing number of passengers are projected to cross multiple time zones. While shift work and jetlag bring a clear disruption of the circadian system and sleep, even “normal” work hours can result in a smoother imbalance of circadian rhythm and sleep deprivation, especially among evening chronotypes. This is because many individuals use alarms to produce wakefulness when sleep would otherwise occur [5].

Other sources of circadian disruption can be unusual photoperiod (polar regions), circadian rhythm sleep (wake disorders [non-24-h sleep-wake disorders], senescence, disease states [Alzheimer’s disease, Smith-Magenis syndrome, Parkinson disease]), and pregnancy, menopause, mental health problems, or medications.

Circadian pathology can be induced by factors related to oscillators such as the uncoupling between the different oscillators inside the SCN caused by aging and the uncoupling between the central and peripheral oscillators or clock gene functional alterations result in circadian disruption or can be induced by factors related to outputs such as nocturnal melatonin suppression and loss of cortisol rhythmicity, which are also chronodisrupters. Many pathological states can be induced or impaired as consequence of circadian disruption [3].

Common circadian rhythm disorders include:

Jetlag or rapid time zone change syndrome: individuals with this syndrome exhibit symptoms that include excessive sleepiness and a lack of daytime alertness in those who travel across time zones.

Shift work sleep disorder: this sleep disorder affects individuals who frequently rotate shifts or work at night.

Delayed sleep phase syndrome (DSPS): this is a disorder of sleep timing. Individuals with DSPS tend to fall asleep very late at night and have difficulty waking up in time for work, school, or social engagements.

Advanced sleep phase disorder (ASPD): this is a disorder in which an individual goes to sleep earlier and wakes earlier than desired. ASPD results in symptoms of evening sleepiness, going to bed earlier (e.g., between 6:00 and 9:00 p.m.) and waking up earlier than desired (e.g., between 1:00 and 5:00 a.m.).

Non-24-h sleep-wake disorder: this disorder frequently affects those that are totally blind because the circadian clock is set by the light-dark cycle over a 24-h period. In non-24-h sleep-wake disorder, the cycle is disturbed. The disorder results in drastically reduced sleep time and quality at night and problems with sleepiness during daylight hours.

Some behavioral and pharmaceutical interventions balance the adverse effects of circadian rhythm and sleep disorders; however, some of the beneficial effects of these interventions may be independent of the circadian system and sleep. Because understanding of the relationships between the healthy phases of the SCN and peripheral clock systems is poorly characterized, clarifying these relationships may help to personalize chronobiotic prescriptions, some of which still require safety and efficacy studies. It is then necessary to compare these interventions and to assess which are most effective and under what circumstances [5].

Currently, it is no longer sufficient to classify health as the potential ability of an organism to cope with the varying effects of the environment without disturbing biologically important functions. We have the resources and a relatively accurate statistical methodology that enables us to assess the maximum and minimum functional capacities of each functional system at any time.

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