**FUTURISTIC TRENDS OF CHRONOPHARMACOLOGY**

**Raj Bala, Prabhjot Kaur and Gautam Raj Puri**

**Author’s details: School of Pharmaceutical Sciences RIMT University Mandi-Gobindgarh**

An obvious physiological characteristic of living organism is the variability of biological phenomenon over time. This variability undergoes rhythmicity at the cellular, organ and systemic level [1-4].

**History**

It has long been known that the physiological phenomena chronopharmacology studies are cyclical. One of the earliest pieces of literature was written in 1797 by Christoph Wilhelm Hufeland, a professor of pharmacology at the Academy of Jena, who noticed that the 24-hour photoperiod is the fundamental rhythm governing bodily activity. Julien Joseph Virey, a French scholar, wrote a significant paper on the biological significance of circadian rhythms in 1814, noting that "all pharmaceuticals are not equally indicated effective given at different hours of the day" [5]. Cyclicality of heart rate (HR) studies (which eventually led to the phenomena of HR variability, or HRV), variations in respiratory rhythm, body temperature, pain perception, and symptom exacerbation came to light in later years. For the discovery of the fundamentals of the biological clock function in studies of fruit flies and their demonstration of the presence of proteins accumulating in cells at night and degrading during the day, Michael Rosbash, Jeffrey C. Hall and Michael W. Young received the 2017 Nobel Prize in Physiology or Medicine. This culminated years of investigation into the significance of biological rhythms in pharmacology and physiology. The Nobel Assembly at Karolinska Institutet stated in the official news release that it has long been understood that all living things, including humans, have inbuilt biological clocks that enable them to adjust and anticipate to the periodic rhythm. How the inner clock adapts our physiology to different phases of the day was explained by the molecular level discoveries of Jeffrey C. Hall, Michael W. Young and Michael Rosbash [6]. Nobel laureates research emphasized the significance of chronobiology and its fundamental importance in the development of chronopharmacology [7].

**Definitions**

The chronopharmacology, is a branch of chronobiology, that deals with the study of pharmacological characteristics and include the time dependency of the drug response. The research of the chronopharmacodynamics (cPD) and chronopharmacokinetics (cPK) and is done in chronopharmacology, which subsequently aids in the creation of the chronopharmaceutical drug delivery system (DDS). Additionally, a lot of medical diseases exhibit daily rhythmicity [8]

Chronopharmacology is a subbranch of pharmacology which focuses on understanding the relationship between biological rhythms and pharmacotherapy, or the timing of administration of drug and its effects [1-3].

**Biological Rhythm**

Biorhythms are self-sustaining physiological phenomena oscillations that are produced and regulated by endogenic "biological clocks" and are distinguished by repeatability. These rhythms are an illustration of how adaptable the body is. They are turned on to coordinate biological and behavioural processes with the external environment's dynamically shifting and predictable conditions, which have an impact on the body's homeostasis.

Period (complete cycle length), mean value (mesor), acrophase (the point in a cycle where the rhythm reaches its maximum value), amplitude (the difference between the mesor and maximum value), and nadir (the point in a cycle where the rhythm reaches its minimum value) are some characteristics of biological rhythms. When the period is taken into account, we can distinguish between ultradian rhythms, which have cycles of varying duration, lesser than 24 hours, lying from one to several seconds (for example, electroencephalographic recordings oscillations, respiratory rate and heart rate) to several hours (for example, the cycle of change of basic sleep stage); and circadian rhythms ("circa"—around; "dies"—day"), which have cycles of about 24 hours, primarily related to photoperiodism (for example Particularly obvious circadian rhythm-controlled physiological and pathological processes.It should be emphasised that endogenous biological rhythm disruptions are linked to the pathophysiology of many diseases, including ulcer disease, bronchial asthma, rheumatic disorders, and depression. Similar to this, it has been shown that certain diseases have a higher probability of developing during particular times of the day. Examples include cardiovascular events (such as myocardial infarction, sudden cardiac death and stroke) in the morning and the worsening of peptic ulcer disease at night. [7].

**The Regulation of Biological Rhythms**

The circulatory system phenomena along with multiple physiological functions, including the behavior, hormone levels, sleep, functions of other body systems, metabolism and body temperature are regulated by the biological clock. The biological clock is hierarchically superior central oscillator which coordinates the activity of other oscillators is the suprachiasmatic nucleus (SCN) that is located bilaterally right above the optic chiasm, in the anterior part of the hypothalamus,. Sunshine mostly modulates the activity of SCN. Through the retinohypothalamic tract (originating from the photosensitive retinal ganglion cells) and from the other tracts: geniculo-hypothalamic tract, tracts leading from the structures of the septum, reticular formation, hippocampus and limbic system, SCN receives the afferent information that autonomically generates a cyclic activity modulated by the afferent signals. Efferent impulsation is transferred to the external oscillators—the target structures of the endocrine, autonomic and immune systems that carry out secondary modulation of the functioning of other bodily systems and adjusting it to the rhythmic changes (mostly the day–night rhythm) of the external environment. Retino-hypothalamic tract, one of the most important tracts that is connected with melatonin secretion from the pineal gland. Melatonin secretion elevates at night while is inhibited by light. In multiple peripheral tissues, melatonin receptors can be found, through which the hormone can exert its effect to modulate the physiological functions. One more important tract is the tract connecting the SCN with the periventricular nucleus of the hypothalamus, connecting the SCN with neurosecretory cells secreting corticoliberin (HPA tract—hypothalamus–pituitary gland–adrenal glands) and other cells controlling the endocrine glands [1,2,3,9,10].

**The Genes that control the Biological Clock**

The cyclicity of the SCN physiological changes is induced by the oscillations at the molecular level in the expression of genes, their transcription factors and the final synthesized proteins, that creates negative feedback loops with neuroendocrine output information. *Clock* (Circadian Locomotor Output Cycles Kaput) and *Bmal1* (Brain-muscle Arnt Like-1) are the two main genes regulating the activity of the biological clock, being the stimulating fragment of the feedback loop and are transcribed and translated early during the day. The resulting CLOCK and BMAL1 proteins undergo heterodimerization, translocated to the cell nucleus, where they bind with specific DNA regions that are the promoter sections of genes *Cry1*, *Cry2* (Cryptochrome) and *Per1*, *Per2*, and *Per3* (Period).  The target genes encode the proteins which is the negative effector limb of the regulation loop. PER and CRY proteins accumulate in the cytoplasm during the next hours and are transported subsequently to the cell nucleus where they act as repressive transcription factors of the CLOCK–BMAL1 complex. PER and CRY proteins are degraded at night, which results in blocking of their inhibiting effect on CLOCK–BMAL1, thus, a new biochemical cycle is initiated [8,11]. The discovery of the basics of circadian functioning of the biological clock and genes controlling it, is connected with environmental conditions (amount of light) adaptation changing on a cyclic basis, was awarded the Nobel Prize in 2017 in Physiology and Medicine [12].

**The Impact of Biological Rhythms on Pharmacology of Diseases**

The best-documented circadian rhythms is the circadian variability of arterial blood pressure (B.P). Decrease in the BP value and heart rate (HR) are observed at night, both in normotensive persons and in most patients with primary arterial hypertension, while their elevation is observed in the morning hours, that is related to engaging in daily life activities. This rhythm is related to the cyclic rise in the morning activity of the plasma renin activity, sympathetic nervous system, secretion of hormones with a pressor effect, elevating the peripheral resistance and accelerating the electrical conduction system automatism of the heart in the morning. In the late morning and early afternoon, B.P reaches its peak values; after that, it declines between 8 p.m. and 2 a.m. when it is usually lowest [13, 14]. Furthermore, in the morning, the fibrinolytic activity of the plasma is reduced, that is connected with elevated tendency to form thrombi at that time. Thus, increased risk of cardiovascular events takes place in the morning period (3–4 h after waking up), such as acute coronary syndromes or strokes. The demonstration of the cyclic activity of the endothelium was found to be an interesting observation, with maximum secretion of nitrogen oxide during the day and in the morning, a physiological homeostatic mechanism counteracting the excessive rise in BP as a result of activity of the mechanisms referred above. On the contrary, the functional prevalence of the parasympathetic part of the autonomic nervous system takes place in the evening and night, with decreased activity of the RAA system, decreased secretion of pressor hormones thus decreasing the BP and HR values [15,16]. The above phenomenon is expressed in clinical terms, by the possibility of differentiation, based on the results of 24-h monitoring of BP changes in patients with primary arterial hypertension, of the “dippers” and “nondippers” subpopulation. In compliance with the observations of chronobiology, the expected fall in systolic (SBP) and diastolic (DBP) arterial tension values by 10–20% in relation to their values recorded during the day is typical for the dippers. Meanwhile, lack of the expected night SBP/DBP dip by at least 10% is a disturbance characteristic for the “nondippers”. On the other hand, a massive decline in SBP/DBP, exceeding 20% of their day values, is typical for the “extreme dippers”.[16,17,18] The phenomenon of “extreme dippers” is also connected with the risk of orthostatic hypotension as well as potential ischemic complications, including optic nerve damage.[18] Evaluation of the chronobiological morning increase in BP (“morning surge”) is also carried out in clinical conditions. Reference literature describes a positive correlation between the “morning surge” phenomenon and development of cardiovascular events as well as organ complications of the primary arterial hypertension. In practice, the value of the “morning surge” is established based on determination of the difference between the mean SBP within 2 h after waking up and the mean of three lowest night values of SBP. According to other recommendations, the “morning surge” is determined on the basis of evaluation of the mean BP from measurements taken 2 h after and 2 h prior to waking up. An excessive increase in the systolic pressure by ≥ 50 mm Hg and/or diastolic pressure by ≥ 22 mm Hg in the morning hours in relation to the mean pressure at night is considered pathological.[19,20]

Primary hypertension is an excellent example of a disease that should be treated in line with chronopharmacotherapy rules to synchronize the changes in the hypotensive drug blood concentration with the 24-h change in arterial hypertension. This procedure enables improving the effectiveness and safety of antihypertensive treatment.[21]Thus, the general, routine recommendations for the chronotherapy of hypertension indicate that antihypertensive drugs should be administered in higher doses during the early-morning postawakening period, when BP is highest, and these agents should be delivered in lesser concentrations during the middle of a sleep, when BP is low. However, the detailed guidelines for the chronotherapy of hypertension depend on the precise characteristics of the hypertensive patient (“dipper”, “nondipper”, or “morning surge” patients).[13,14,15,16] Several clinical studies have shown that administration of RAA-system-inhibiting drugs (angiotensin-converting enzyme inhibitors, angiotensin II AT1 receptor antagonists) at night—i.e., at the time of expected decreased activity—in nondipper patients translated to better hypertension control in comparison with administration of such drugs in the morning. Similar results have been obtained for thiazide diuretics applied in hypotensive monotherapy in the evenings. On the other hand, in the case of beta-adrenolytic drugs, it has been proven that administration of such drugs in the morning improves the efficiency of hypotensive treatment (due to the increase in catecholamines and expression of adrenergic receptors at this time of the day, as mentioned above) in comparison with evening dosage. It must be also noted that the dependency of change in hypertension therapy effectiveness depending on the timing of administration was not demonstrated in the case of dihydropyridine calcium channel blockers, most probably due to their rather long biological half-life.[1,16,21,22]

The next adequate example illustrating the role of chronobiology is the use of melatonin and drugs modulating melatonin receptors in the treatment of insomnia. As mentioned above, melatonin is a hormone produced in the pineal gland under control of the circadian system in the hypothalamic suprachiasmatic nucleus (SCN). Normally, the melatonin level is low throughout the daytime, and rises in the evening as bedtime approaches. The plateau phase of melatonin secretion occurs during the night hours, and then declines by the typical wake time around dawn. With the evening melatonin rise, the circadian arousal level declines, reducing the homeostatic drive of daily activity. In this manner, the melatonin rise facilitates sleep onset and additionally reinforces the timing of the circadian system. It rationalizes the administration of melatonin as a chronobiological hypnotic drug.[23,24] Further, other melatonin receptor agonists (ramelteon, tasimelteon) are used to treat insomnia (late sleep induction) in selected European countries, Japan, and the USA. In addition, agomelatine, used as an antidepressant, was evaluated for improving circadian rhythm and to induce evening sleep in patients with disturbed 24 h sleep–wake rhythms (e.g., in the course of dementia and depression).[25,26]

**Mechanism of Chronopharmacology:**

Circadian and other rhythmic changes in biological susceptibility and response of organisms to a large variety of physical and chemical agents including medications and foods are rather common phenomena. Time-related differences in drug effects depend upon endogenous circadian rhythms, which include metabolic pathways. In addition, chronopharmacology investigates drug effects on parameters (e.g. circadian period, peak time, amplitude, and adjusted mean) used to characterize biological rhythms. A better understanding of periodic and thus predictable changes in drug effects can be attained by consideration of complementary concepts:-
a.       The chronokinetics for a drug, i.e. dosing time-dependent and predictable (rhythmic)  changes in parameters used to characterize the pharmacokinetics (bioavailability) of a drug, e.g. Cmax, tmax, AUC, and t1/2;

b.      The chronesthesy, i.e. rhythmic changes in susceptibility of the target biosystem to this drug, including CR in pharmacodynamic processes; and
c.       The chronergy, i.e. the drug-integrated overall effect.

Chronopharmacology involves both the investigation of drug effects as a function of biologic timing and the investigation of drug effects upon rhythm characteristics.

Circadian changes in the effects of various chemical agents have been documented: histamine, sodium salicylate, acetylcholine, halothane, prostaglandine F, reserpine, cyproheptadine, ethanol, insulin, chlorothiazide, oxymetholone, orciprenalin and SCH 1000 (bronchodilators), indomethacin, ACTH, cortisol and various synthetic corticosteroids.

Chronopharmacology is useful to solve problems of drug optimization, i.e. to enhance the desired efficiency or to reduce its undesired effects. In the human organism (among other animal species) the metabolic fate of a pharmacologic agent (as well as that of a nutrient) is not constant as a function of time. Thus, the chronobiological approach of pharmacologic phenomena involves a lesser risk of errors and/or false information than the conventional homeostatic approach.

One of the aims of chronopharmacology refers to the use of a chronopharmacological approach to clinical treatment so as to enhance both effectiveness and tolerance of a drug by determining the best biological time for its administration.[27]

**Factors Affecting Chronopharmacology:**

To optimize chronotherapeutic schedules (designs), we examined the interindividual differences in chronopharmacologic effects of drugs with consideration of the following three factors:

(a) Inherited factors of direct relevance to chronopharmacology (genetic variability, gender-related differences) as well as age-related differences;

(b) Interindividual difference in chronoeffectiveness related to disease (e.g., various types and stages of cancer, affective disorders, etc.) as well as to drug-dependent alteration (phase shifts, distortion) of biological rhythms; and

(c) Means to solve problems resulting from the need of individualization in chronotherapy. These involve the use of circadian marker rhythms (MR) whose characteristics (peak or trough time, amplitude, etc.) can be precisely quantified and thus are applicable as a reference system for physiologic, pathologic, pharmacologic and therapeutic uses.

The MR has to be specific and pertinent and must be easily monitored and documented. This approach can be further advanced by the use of a battery of MRs rather than a single MR. Other suggested means relate to the fact that chronobiotics (agents capable of influencing parameters of a set of biological rhythms) should be considered (e.g., corticoids and adrenocorticotropic hormone) and/or to the subject's synchronization should be enforced by "conventional" zeitgebers (e.g., bright light, physical activity).[27]

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