

# FUTURISTIC TRENDS OF CHRONOPHARMACOLOGY

## Abstract

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].

**Keywords:** Chronopharmacology, physiological, biological, cyclical.

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## **I. 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, it was observed that the effectiveness of pharmaceuticals varies depending on the time of day they are administered [5]. Cyclicity 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. In recognition of their groundbreaking research on the biological clock function, In 2017, the Nobel Prize in Physiology or Medicine was presented to Michael Rosbash, Jeffrey C. Hall, and Michael W. Young. Their work, which focused on studies involving fruit flies and the revelation of proteins accumulating in cells during the night and degrading during the day, significantly advanced our understanding of circadian rhythms and their molecular underpinnings. This culminated years of investigation into the biological rhythms significance in pharmacology and physiology. The Nobel Assembly at Karolinska Institute 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. The molecular-level discoveries of Jeffrey C. Hall, Michael W. Young, and Michael Rosbash explained how our inner clock adapts our physiology to various phases of the day [6]. The research conducted by Nobel laureates Michael Rosbash, Jeffrey C. Hall, and Michael W. Young emphasized the critical importance of chronobiology and its fundamental role in the advancement of chronopharmacology [7].

## **II. DEFINITIONS**

Chronopharmacology, as a subset of chronobiology, is a field of study that focuses on examining the pharmacological properties of drugs, specifically considering the time-dependent aspects of drug responses. It involves investigating how the timing of drug administration can influence the efficacy, safety, and overall impact of medications on the body's biological rhythms and physiological processes. 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].

## **III. 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].

#### IV. THE REGULATION OF BIOLOGICAL RHYTHMS

In addition to numerous physiological functions, the circulatory system phenomena, includes the behavior, hormone levels, sleep, functions of other body systems, metabolism and body temperature are influenced by the biological clock. The suprachiasmatic nucleus (SCN), located bilaterally, above the optic chiasm, in the anterior part of the hypothalamus, serves as the central oscillator with hierarchical authority over other oscillators in the biological clock system. Sunshine mostly modulates the activity of SCN. The suprachiasmatic nucleus (SCN), a crucial component of the circadian system, receives afferent (incoming) information from various sources, which influences its cyclic activity. These afferent signals are transmitted through different neural pathways, including:

- 1. Retinohypothalamic Tract:** Emerging from photosensitive retinal ganglion cells in the eyes, this tract provides direct input to the SCN, conveying information about light levels in the environment. It helps synchronize the body's internal clock with the external light-dark cycle.
- 2. Geniculo-Hypothalamic Tract:** Another pathway, the geniculo-hypothalamic tract, also contributes to SCN's afferent inputs. It conveys visual information to the SCN but through a different route.
- 3. Tracts from Various Brain Structures:** Information is received from tracts originating in structures such as the septum, reticular formation, hippocampus, and the limbic system. These brain regions are involved in various aspects of cognition, emotion, and memory.

The SCN processes and integrates the afferent signals it receives, resulting in the generation of efferent (outgoing) signals. These efferent signals are then transmitted to external oscillators, which are target structures located throughout the body. These external oscillators belong to the endocrine, autonomic, and immune systems. They carry out a

secondary modulation of the functioning of various bodily systems, helping to adjust them to the rhythmic changes dictated by the circadian system.

In essence, the SCN serves as the central pacemaker for circadian rhythms in the body. It receives input from multiple sources to help maintain synchronization with the external environment and subsequently communicates with various systems to coordinate and modulate their functions in a rhythmic manner. This intricate network of communication and regulation is crucial for ensuring that physiological processes occur at optimal times and are synchronized with the daily cycle (mostly the day–night rhythm) of the external environment. Retino-hypothalamic tract, one of the most important tracts that is related to the release of melatonin 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. Another significant pathway involves the connection between the suprachiasmatic nucleus (SCN) and the periventricular nucleus of the hypothalamus. This connection links the SCN to neurosecretory cells responsible for the secretion of corticotiberin (part of the HPA axis – hypothalamus-pituitary gland-adrenal glands) and other cells that regulate endocrine gland function [1,2,3,9,10].

## V. THE GENES THAT CONTROL THE BIOLOGICAL CLOCK

The oscillations induce the The periodicity of physiological changes in the suprachiasmatic nucleus (SCN) at the molecular level in the genes expression, their transcription factors and the final synthesized proteins, that generates negative feedback loops with neuro-endocrine output information. *Bmal1* (Brain-muscle Arnt Like-1) and *Clock* (Circadian Locomotor Output Cycles Kaput) are the two important genes that regulate biological clock activity, being the feedback loop stimulating fragment, undergo transcription and translation in the early part of the day. The resultant BMAL1 and CLOCK proteins undergo heterodimerization, translocated to the nucleus of the cell, bind with specific DNA regions which are the promoter sections of genes *Cry1*, *Cry2* (Cryptochrome) and *Per1*, *Per2*, and *Per3* (Period). The target genes encode proteins that constitute the negative regulatory component within the feedback loop. In the cytoplasm, PER and CRY proteins gradually accumulate over the following hours, and they are subsequently transported to the cell's nucleus, where they function as repressive transcription factors for the CLOCK-BMAL1 complex. During the night, PER and CRY proteins undergo degradation, which leads to the removal of their inhibitory effect on CLOCK-BMAL1, initiating a new biochemical cycle. [8,11]. The Nobel Prize in Physiology and Medicine was conferred in 2017 for the revelation of the fundamental workings of the biological clock and the genes that govern it. This breakthrough is intricately tied to the adaptation of living organisms to cyclic changes in environmental conditions, particularly variations in light levels. [12].

## VI. 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 most patients with primary arterial hypertension and normotensive persons, but their elevation is seen in the morning hours, that is related to engaging in daily life activities. This rhythm is associated with the cyclic increase in morning activity of plasma renin, the

sympathetic nervous system, and the secretion of hormones that have a pressor effect. These factors collectively lead to elevated peripheral resistance and an acceleration in the electrical conduction system's automatism within the heart during the morning. During the late morning and early afternoon, blood pressure reaches its highest levels, and subsequently decreases between 8 p.m. and 2 a.m., typically reaching its lowest point during this period. [13, 14]. Moreover, during the morning hours, the fibrinolytic activity of plasma decreases, leading to an elevated propensity for thrombus formation during this time. Consequently, an increased risk of cardiovascular events, such as acute coronary syndromes or strokes, occurs in the morning period, typically about 3 to 4 hours after waking up. The observation of the cyclic activity of the endothelium, where the highest secretion of nitric oxide occurs during the daytime and in the morning, is a fascinating finding. This physiological homeostatic mechanism helps counteract the excessive increase in blood pressure resulting from the mechanisms mentioned earlier. Conversely, the functional predominance of the parasympathetic branch 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, the potential for distinguishing between subpopulations of individuals with primary arterial hypertension, specifically those categorized as "dippers" and "nondippers," can be determined through a 24-hour monitoring of blood pressure changes. In line with observations from the field of chronobiology, it is common for "dippers" to experience a typical decrease in systolic (SBP) and diastolic (DBP) blood pressure values, typically ranging from 10% to 20%, compared to their daytime measurements. Conversely, the absence of this expected nighttime dip in SBP/DBP by at least 10% is a defining characteristic of "nondippers." On the other hand, "extreme dippers" are characterized by a substantial drop in SBP/DBP, exceeding 20% of their daytime values. [16,17,18] The presence of "extreme dippers" is also associated with an increased risk of orthostatic hypotension and potential ischemic complications, which may include damage to the optic nerve.[18] The assessment of the chronobiological rise in blood pressure in the morning, often referred to as the "morning surge," is conducted in clinical settings. The scientific literature indicates a positive correlation between the "morning surge" phenomenon and the occurrence of cardiovascular events and organ complications in individuals with primary arterial hypertension. In practical terms, the "morning surge" is determined by calculating the difference between the average systolic blood pressure (SBP) measured within two hours after waking up and the average of the three lowest nighttime SBP values. Alternatively, according to other guidelines, the "morning surge" can be assessed by examining the mean blood pressure readings taken two hours after and two hours before waking up. An abnormal elevation in systolic pressure of 50 mm Hg or more and/or diastolic pressure of 22 mm Hg or more during the morning hours when compared to the nighttime mean pressure is regarded as a pathological indicator. [19,20]

Primary hypertension serves as a prime illustration of a condition that benefits from treatment following the principles of chronopharmacotherapy. This approach aims to align the fluctuations in the concentration of hypotensive drugs in the bloodstream with the 24-hour variations in arterial blood pressure. This method facilitates enhancing the efficacy and safety of antihypertensive therapy.[21] As a result, the standard guidelines for chronotherapy in the treatment of hypertension suggest that antihypertensive medications should be given at higher doses during the early-morning period after waking when blood pressure is at its peak, while they should be administered at lower concentrations during the middle of the sleep cycle when blood pressure is lower. However, it's important to note that the specific

recommendations for chronotherapy in hypertension management may vary depending on the particular characteristics of the hypertensive patient, whether they fall into categories such as "dipper," "nondipper," or "morning surge" patients. [13,14,15,16]

Numerous clinical studies have revealed that administering drugs that inhibit the renin-angiotensin-aldosterone system (such as angiotensin-converting enzyme inhibitors and angiotensin II AT1 receptor antagonists) during the nighttime, coinciding with the expected decrease in physiological activity in nondipper patients, leads to better management of hypertension compared to administering these drugs in the morning. Similarly, similar positive outcomes have been observed when using thiazide diuretics as standalone hypotensive therapy in the evening. Conversely, when it comes to beta-adrenolytic drugs, research has demonstrated that administering them in the morning enhances the effectiveness of hypotensive treatment. This is attributed to the increase in catecholamines and the expression of adrenergic receptors during the morning hours, as mentioned earlier. It's important to note that this dependency on the timing of administration hasn't been demonstrated for dihydropyridine calcium channel blockers, likely because of their relatively long biological half-life. [1,16,21,22]

Another compelling example that underscores the significance of chronobiology is the utilization of melatonin and medications that target melatonin receptors in the treatment of insomnia. As mentioned earlier, melatonin is a hormone produced by the pineal gland, and its release is regulated by the circadian system within the hypothalamic suprachiasmatic nucleus (SCN). Typically, melatonin levels remain low during daylight hours, begin to increase in the evening as bedtime approaches, reach a plateau during the night, and then naturally decline as dawn approaches, corresponding to the usual wake-up time.

The rise in melatonin during the evening has the effect of reducing the circadian arousal level, diminishing the body's drive for daytime activities. This elevation in melatonin plays a crucial role in facilitating the initiation of sleep and further reinforces the synchronization of the circadian system. This rationale supports the use of melatonin as a chronobiological sleep-inducing medication. [23,24]

Moreover, in certain European countries, Japan, and the USA, other melatonin receptor agonists like ramelteon and tasimelteon are employed to address insomnia characterized by difficulties in initiating sleep later in the evening. Additionally, agomelatine, which is primarily used as an antidepressant, has been assessed for its potential to enhance circadian rhythms and induce nighttime sleep in individuals with disrupted 24-hour sleep-wake patterns, often observed in conditions such as dementia and depression. [25,26]

## **VII. MECHANISM OF CHRONOPHARMACOLOGY**

Circadian and other rhythmic variations in the biological sensitivity and response of organisms to a wide range of physical and chemical agents, including medications and dietary substances, are quite prevalent occurrences. These time-dependent variances in drug impacts are influenced by internal circadian rhythms, which encompass various metabolic processes. Furthermore, chronopharmacology explores how drugs affect parameters (such as circadian period, peak time, amplitude, and adjusted mean) that are employed to describe biological rhythms.

To gain a deeper insight into these periodic and therefore foreseeable fluctuations in drug effects, it is valuable to consider complementary concepts. In the field of chronopharmacology, several key concepts play a crucial role in understanding the time-dependent effects of drugs and optimizing their use:

- 1. Chronokinetics:** This term refers to the dosing time-dependent and predictable (rhythmic) changes in parameters used to characterize the pharmacokinetics of a drug. These parameters may include  $C_{max}$  (maximum concentration),  $t_{max}$  (time to reach maximum concentration), AUC (area under the concentration-time curve), and  $t_{1/2}$  (half-life). Chronokinetics helps us understand how the body's ability to absorb, distribute, metabolize, and eliminate a drug varies with the time of administration.
- 2. Chronesthesia:** Chronesthesia involves rhythmic changes in the susceptibility of the target biological system to a drug. This encompasses circadian rhythms in pharmacodynamic processes, which influence how a drug interacts with its target receptors or pathways within the body.
- 3. Chronergy:** Chronergy represents the integrated overall effect of a drug, taking into account its pharmacokinetics and pharmacodynamics over time. It considers the cumulative impact of a drug's administration on a biological system.

Chronopharmacology investigates drug effects as they relate to biological timing and how drugs influence rhythm characteristics. It recognizes that circadian changes in the effects of various chemical agents, including medications and substances, have been observed. Some examples of substances exhibiting circadian variations in their effects include histamine, salicylate, acetylcholine, and various drugs like corticosteroids and bronchodilators. Chronopharmacology is a valuable approach to optimizing drug therapy. It aims to enhance a drug's desired effectiveness while minimizing its undesired side effects. Unlike a conventional homeostatic approach, which assumes constant responses, the chronobiological approach acknowledges that the metabolic fate of a drug (or nutrient) varies throughout the day. Consequently, it reduces the risk of errors and provides more accurate information. One of the primary goals of chronopharmacology is to use this knowledge to determine the best biological time for administering drugs in clinical treatment. By doing so, it seeks to improve both the effectiveness and tolerability of medications within the human organism and other animal species, recognizing the importance of timing in drug therapy [27].

## VIII. FACTORS AFFECTING CHRONOPHARMACOLOGY

To enhance the optimization of chronotherapeutic regimens, we have examined the individual variations in the chronopharmacological effects of drugs, taking into account the following three factors:

- 1. Inherited Factors:** These factors include genetic variability, gender-related differences, and age-related variations that directly influence chronopharmacology. Genetic makeup, gender, and age can all impact how an individual responds to chronotherapy.
- 2. Disease and Drug-Related Factors:** Interindividual differences in chronoeffectiveness can be linked to the specific disease being treated, such as various types and stages of cancer or affective disorders. Additionally, drug-induced alterations, such as phase shifts

or distortions in biological rhythms, contribute to variability in drug responses among individuals.

- 3. Individualization in Chronotherapy:** To address the need for individualization in chronotherapy, we explore methods to tailor treatment to each patient's unique characteristics. This includes the use of circadian marker rhythms (MR) as reference points for physiological, pathological, pharmacological, and therapeutic purposes. These MRs should be specific, relevant, easily monitored, and well-documented. Furthermore, employing a set of MRs rather than relying on a single MR can enhance precision.

Additional strategies involve considering chronobiotics, which are substances capable of influencing parameters of various biological rhythms (e.g., corticoids and adrenocorticotrophic hormone). Furthermore, efforts to synchronize an individual's biological rhythms can be undertaken using conventional zeitgebers, such as exposure to bright light or engaging in physical activity.

In summary, optimizing chronotherapeutic schedules involves accounting for individual differences related to genetics, gender, age, disease, drug-induced alterations in rhythms, and tailoring treatment through the use of specific, easily monitored circadian marker rhythms, potentially in combination with chronobiotics and zeitgebers, to achieve the best therapeutic outcomes. [27]

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