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CHRONOPHARMACOLOGY AND PERSONALIZED MEDICINE: CURRENT CONCEPTS AND FUTURE PERSPECTIVES

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ABSTRACT

Chrono pharmacology is a field studying the interaction between biological rhythms, like the circadian rhythm, and the pharmacokinetics (drug absorption, distribution, metabolism, and excretion) and pharmacodynamics (how drugs affect the body) of medications. It emphasizes aligning medicine administration with the body's natural cycles to ameliorate remedial issues and reduce side effects. Circadian rhythms influence drug behaviour and impact systems like the immune, cardiovascular, and nervous systems, affecting drug effectiveness. For example, antihypertensive medications may work better when taken at night, and chemotherapy may be more effective when timed with tumour cell growth cycles. Antidiabetic medicines also show better results when aligned with insulin production. Chrono pharmacology aims to optimize drug treatment by considering the timing of administration, enhancing benefits while minimizing side effects. This approach, known as chronotherapy, is gaining interest in personalized medicine, which tailors treatment plans to individual circadian rhythms, age, and lifestyle. Though promising, chrono pharmacology is still developing. further exploration is required to understand its mechanisms and upgrade clinical guidelines for precise medicine timing, with the eventuality to revise treatment and give safer, more effective curatives.

INTRODUCTION

Chrono pharmacology is a field of science focusing on studying the effect of biological rhythms on pharmacotherapy, i.e., a branch of pharmacology studying the dependencies between the timing of drug administration and its effect [1]. This emerging area of study explores how the circadian rhythms, which regulate various physiological processes, can impact drug pharmacokinetics and pharmacodynamics [2]. Currently, therapy individualization in specific patients is based on consideration by the prescribing doctor of the age, sex, and individual physio- and pathophysiological conditions (existence of concomitant diseases) to anticipate the potential onset of drug interactions resulting from application of polypharmacotherapy-i.e., the patient's pharmacokinetic profile (determined by way of evaluation of the phenotypic response to the administered drug or direct genotyping).[3] The body's circadian rhythm can be used to forecast a drug's pharmacological effects when it is given. It is conceivable to associate with both time and bodily activities. The maximum efficacy and least number of toxic effects of a drug can be accomplished if it is given at the proper time, hat is, the correct medication in the correct form at the correct dose at the correct time. This is analogous to how sleep-awake; feed appetite, happiness, and depression are controlled by natural timepieces. thus, the drug works in musicale with the natural timepiece [4]. The ultimate goal of chrono pharmacology is to design drug dosing schedules that align with the body's natural biological rhythms, thereby enhancing drug efficacy and safety while reducing adverse reactions [5].

1. CONCEPT OF CHRONO PHARMACOLOGY

Chronobiology is the branch of science that examines periodic phenomena in living organisms and their adaptation to biological rhythms. Under the impact of time, three disciplines are considered in medicine. Chronophysiology, Chrono pathology and Chrono pharmacology. Chrono pharmacology is the science that deals with the optimization of drug dose that promotes efficacy and minimizes the adverse effects by taking medications about the biological rhythm. Simply

put, medicines can be beneficial and have fewer side effects if we take them by our body clock [6].

There are five divisions under Chrono pharmacology:

1.1 Chrono therapeutics

Administration of drugs according to natural rhythm to maximize pharmacological effects and minimize side effects. The finding that every metabolic event experiences rhythmic fluctuation in time is essentially what this refers to. It is predicated on the discovery that many medications' pharmacokinetics and pharmacologic sensitivities have an important association with the peak-to-trough periodic action in clinical manifestations and comorbidities. Traditionally, medications have been prescribed at regular intervals across the day in an attempt to keep consistent drug concentration over the course of a 24-hour cycle.[7]

1.2 Chrono kinetics

deals with the study of the temporal changes in the pharmacokinetics of the medicines with respective time. Study of absorption, distribution, metabolism, and excretion of drugs according to the time of the day or year. Chrono pharmacokinetics is the study of how drugs are absorbed, distributed, metabolized, and excreted over time.

1.3 Chromesthesia

The cyclic changes in the vulnerability or sensitivity of a target system‖ are explained by chromesthesia. In that it deals with the physiological and biochemical changes brought on by a medicine based on the time of administration, chromesthesia is in many respects comparable to the area of pharmacodynamics. For instance, variations in the degree of membrane permeability or variations in how the cell membrane reacts to chemicals used in cellular communication (i.e., receptors on the surface of brain cells) occur over generally anticipated time periods [8,9].

1.4 Chronergy

Rhythmic changes of both the asked and undesired effects on the organism as a whole. This field of research considers both how the time of day may affect a drug's effects as well as how the drug themselves may affect an organ's biological rhythm. In order to evaluate how a drug affects a person as a whole, Chronergy, then, synthesizes data from chronopharmacokinetic and chromesthesia. Although it receives relatively less attention in the circulation, this subject is gradually becoming one of the more well-liked subspecialties of Chrono pharmacology [10].

1.5 Chronotoxicology

Chronotoxicology is the study of the adverse goods of chemicals on living organisms in relation to their circadian measures. Particularly, it examines toxic ants' chrono toxicity, i.e., periodic changes in sensitivity of living organisms to toxic ants [11].

2. CHRONO PHARMACOLOGY – A BRIEF THEORETICAL OVERVIEW

2.1 A short historical review and present status in pharmacology.

A circadian cycle was first observed in the 18th century in the movement of plant leaves by the French scientist Jean-Jacques d'Or Tous de Marian. In 1751 Swedish botanist and naturalist Carl Linnaeus (Carl von Linné) designed a flower clock using certain species of flowering plants. By arranging the selected species in a circular pattern, he designed a clock that indicated the time of day by the flowers that were open at each given hour. For example, among members of the daisy family, he used the hawk's beard plant which opened its flowers at 6:30 am and the hawk bit which didn't open its flowers until 7 am. Chrono pharmacology utilizes knowledge of biological rhythms to develop optimal pharmacotherapeutic approaches. A fundamental physiological characteristic of living organisms is the rhythmic nature of biological processes, which vary over time rather than remaining constant. These rhythms manifest at systemic, organ, and cellular levels and are driven by internal "biological clocks." These self-sustaining oscillations are characterized by regularity and reflect the body's adaptive ability to synchronize its biological and behavioural functions with the changing and predictable conditions of the external environment, thereby maintaining homeostasis. [12]

2.2 Characteristics of biological rhythms:

Examples of Physiological Phenomena and Pathophysiological Conditions with a Chronobiological Basis.

Biological measures are characterized by several crucial features: period, which is the duration of one full cycle; mean value (meson), representing the average position of the rhythm; amplitude, the meson, which represents the average value, the Acre phase, which is the time at which the maximum value occurs during a cycle, and the nadir, which refers to the time when the rhythm reaches its minimum value. These include rapid oscillations seen in electroencephalographic (EEG) recordings, heart rate, and respiratory rate, as well as the basic sleep stage transition cycle, which typically lasts a few hours. These rhythms are largely governed by the light-dark cycle (photoperiodism) and regulate key physiological functions, including the sleep-wake cycle, core body temperature, secretion of various hormones, fluctuations in arterial blood pressure, and immune system efficiency. The physiological and pathophysiological processes influenced by circadian rhythms are particularly noticeable and can impact a wide range of bodily functions, from hormone secretion to cardiovascular and immune responses. These rhythms are illustrated in Figure 2. [13]

2.3 The regulation of biological rhythms

Genes Involved in Controlling the Biological Clock.

The circulatory system, along with various physiological functions such as behaviour, hormone levels, sleep, body temperature, and metabolism, is regulated by the biological clock. The suprachiasmatic nucleus (SCN) is the central "biological clock," or primary oscillator, that coordinates the activity of other peripheral oscillators in the body. Located bilaterally in the anterior part of

the hypothalamus, just above the optic chiasm, the SCN plays a critical role in synchronizing biological rhythms. The activity of the SCN is primarily told by light, with incoming signals modulating its function. The SCN receives afferent information through the retinohypothalamic tract, which originates from photosensitive retinal ganglion cells, as well as from other tracts, including the geniculo-hypothalamic tract and pathways from regulate the SCN's cyclic activity, which autonomously generates rhythmic patterns. Efferent impulses from the SCN are transmitted to external oscillators-target structures in the autonomic, endocrine, and immune systems. These systems further adjust the functioning of various body systems, aligning them with the rhythmic changes of the external environment, particularly the day-night cycle. [14,28]

2.4 The impact of biological rhythms on pharmacology of selected diseases

The most well-documented circadian rhythms include the variability in arterial blood pressure (BP), which exhibits a predictable pattern in both normotensive individuals and those with primary arterial hypertension. BP and heart rate (HR) generally drop at night and increase in the morning, reflecting the body's medication for daytime activity. This rhythm is primarily driven by the cyclic increase in morning activity of the sympathetic nervous system, along with elevated plasma renin activity and the secretion of pressor hormones that increase peripheral vascular resistance and enhance the automaticity of the heart's electrical conduction system. As a result, blood pressure peaks in the late morning and early afternoon, then declines in the evening, reaching its lowest point between 8 p.m. and 2 a.m

In discrepancy, the evening and night are periods dominated by the parasympathetic nervous system, which leads to a reduction in pressor hormones and dropped activity of the renin-angiotensin-aldosterone (RAA) system, resulting in lower blood pressure and heart rate. Clinically, these circadian patterns can be used to categorize patients with hypertension into two distinct groups: "dippers" and "nondippers". [15]

3. MERITS OF CHRONO PHARMACOLOGY

- It prohibits higher than required dosing of each class of drug.
- It decreases unnecessary side effects of a drug and thereby helps to reduce the duration of hospitalization.
- It generates usage of the medicine most suitable and the value of the medicine is an increase.

Reduced Adverse Effects:

By timing drug administration to avoid periods of heightened sensitivity, chrono pharmacology minimizes side effects. For instance, chemotherapy drugs can be scheduled to reduce toxicity while maintaining effectiveness.

Personalized Medicine:

Chrono pharmacology supports individualized treatment plans by considering each patient's circadian rhythm, lifestyle, and genetic factors. This makes therapy more tailored and precise [16].

4. CHRONO PHARMACOKINETICS

Chrono pharmacokinetics refers to dosing time-dependent and predictable rhythmic variations in drug pharmacokinetics, affecting bioavailability.

4.1 Absorption chrono pharmacokinetics

The circadian rhythm of the gastrointestinal tract, which controls gastrointestinal physiology, cell proliferation, motility, digestion, absorption, electrolyte balance, and intestinal barrier integrity, affects the pharmacological action of orally delivered medications. The physicochemical characteristics of the active ingredient, physiological variables, and potential concurrent pathophysiological diseases all affect how quickly an object is absorbed. The diurnal pattern of gastric pH, which controls medication ionization and solubility, shows that peak acid production occurs just before midnight. Drug bioavailability depends on transport proteins in enterocytes' apical membranes, which undergo 24-h changes. Absorption rates are higher during the day, particularly in the morning and early afternoon, due to increased visceral blood flow. Lipophilic drugs are absorbed more rapidly in the morning, resulting in higher "C max" and shorter "T max" during morning administration [17].

4.2 Distribution chrono pharmacokinetics

The distribution stage of drugs is influenced by rhythmically changing physiological phenomena. It depends on blood flow, drug binding, and morphotic elements of blood, including erythrocytes and plasma proteins. Circadian variations in cardiac output and visceral flows show that daytime activities are when medication distribution is greatest. Blood proteins and tissues also experience circadian fluctuations. Transcortin affects hormone interactions because it has a lower ability to bind endogenic and exogenic steroids at night and in the morning and a higher capacity at 5 p.m. Plasma concentrations of albumin and alpha-1-acid glycoproteins are highest in the afternoon and lowest at night, indicating an increase in free fraction at night [18].

4.3 Metabolism chronopharmacokinetics

Drug metabolism processes are influenced by circadian fluctuations, with the detoxification of drugs and other xenobiotics involving three stages. Phase I involves drug biotransformation, which involves oxidases, reductases, and hydroxylases. Phase II involves conjugating drugs to hydrophilic molecules, increasing solubility, and facilitating excretion into urine, bile, and feces. Phase III involves transporting metabolites outside the cell into body fluids. The liver is the most important physiological site of drug transformation, but it also occurs in extrahepatic tissues. Hepatic clearance depends on hepatic blood flow, intrinsic clearance, and the size of the free fraction of the drug. Circadian fluctuations in drug concentration are particularly

noticeable when administered intravenous infusions [19].

4.4 Excretion chronopharmacokinetics

Rats with experimental chronic bile drainage subjected to a regular light cycle have dramatically increased bile secretion. The renal blood flow (RBF), glomerular filtration rate (GFR), tubular secretion and reabsorption, urine flow, and urine pH are the factors that control how the kidneys clear the majority of water-soluble drug metabolites. These phenomena exhibit circadian oscillations, with GFR reaching its maximum levels throughout the day and falling off at night [20].

5. CHRONOPHARMACODYNAMICS

Chromesthesia refers to rhythmic and temporally predictable alterations in a target biological system's susceptibility to a drug, which cannot be explained by chronopharmacokinetic changes. Although they have long-term, potentially clinical benefits, only a few patients (20%–30%) are estimated to have a positive response to PD-1/PD-L1 blockade therapy, and primary or acquired resistance may lead to tumour progression in patients with a clinical response. The circadian expression of PD-1 is observed in TAMs obtained from B16 melanoma-bearing mice. DEC2, an element of circadian timepiece, rhythmically suppresses NF- kB- intermediated transactivation of Pdcd1 gene, garbling PD- 1, thereby governing its quotidian expression in TAMs. The antitumor efficacy of BMS-1, a small molecule inhibitor of PD 1/PD-L1, is enhanced by administering the drug at the time of day when PD-1 expression increased on TAMs. Identification of the diurnal expression of PD-1 on TAMs may be useful for selecting the most appropriate time of day to administer PD-1/PD-L1 inhibitors. [21]

6. APPLICATONS OF CHRONO PHARMACOLOGY

• Theophylline was one of the first drugs for which daily variations in its pharmacokinetics were reported. Numerous research findings indicated that Theophylline might be dosed higher during the night than during daytime hours, or even a single evening dose might be used--to overcome the nocturnal decrease in pulmonary function adequately.18 Clinical evidence suggests that terbutaline, a beta 2-sympathomimetic, has circadian phase dependent pharmacokinetics and effects on peak expiratory flow. Oral prednisone is much more effective in improving several features of nocturnal asthma and response to inhaled β-2 agonists when administered at 3 PM rather than 8 AM [22].

• Cardiovascular disorders, such as hypertension, angina, heart attack, and stroke, have distinct patterns of illness. Hypertensive patients' blood pressure increases rapidly in the morning, peaks in the middle to late hours, decreases in the evening, and is lowest when sleepers sleep. Heart attack risk is highest during early morning hours. Antihypertensive products are currently available on the market that releases drugs during the vulnerable hours of 6 A.M to noon after medication administration at 10 P.M. These products are chronotherapeutic medications with new drug delivery mechanisms [23].

Antineoplastic drugs cause cytotoxic effects on both healthy and diseased tissues. The biological rhythms of healthy and tumour cells can influence their susceptibility to these agents. Correct timing of drug treatment can reduce host toxicity, increase drug tolerance, and improve tumour management. Drug properties, DNA and RNA synthesis, translational activity, and mitotic activity also affect tumour cell susceptibility. The timing of drug administration significantly impacts cancer treatment success [24].

7. CHALLENGES FOR CHRONO PHARMACOLOGY

Challenges for chrono pharmacology arise from the complexity of considering the cyclical nature of biological phenomena in drug development and optimization. Despite the potential benefits of tailoring drug delivery based on biological rhythms, there are several hurdles that researchers and health-care professionals must address:

• Lack of Translation Research: Chrono pharmacology is an evolving field, and there is still a relatively limited amount of research conducted in this area. Much of the current knowledge comes from studies on rodents, and translating these findings to humans is non-trivial due to the species-specific nature of drug metabolism and transport. As a result, there may be gaps in our understanding of the full extent of the impact of biological rhythms on drug metabolism and therapeutic responses [1, 25,27].

• Optimized Drug Dosing Schedules: Developing and implementing optimized drug dosing schedules based on an understanding of chrono pharmacology is a complex task. It requires considering individual variations in circadian rhythms, disease conditions, and the specific pharmacokinetic profiles of drugs [26].

• Clinical Implementation: Integrating chrono pharmacology into clinical practice may present logistical challenges. Health-care providers need to consider patient adherence to dosing schedules, potential changes in patient routines, and the availability of chronotherapeutic drug formulations [25,27].

8. FUTURE DIRECTIONS

8.1. Chronotherapy in personalized medicine

Chronotherapy in personalized medicine refers to the practice of administering medications or treatments at specific times of day to optimize their efficacy and reduce potential side effects. This approach takes into account the natural circadian rhythms and biological variations that influence how our bodies respond to different treatments. The goal of chronotherapy is to tailor medical interventions to an individual's unique biological clock, thereby improving treatment outcomes and overall patient health.

8.2 Chrono pharmacology in drug development

Novel chemical entities often fail in drug development due to liver toxicity and cardiac safety concerns. QT prolongation, often associated with blockade of the K+ channel and torsade des pointes, is the most common cause of drug withdrawal. Circadian rhythm influences cardiac repolarization through Krüppel-like factor 15, suggesting a time-of-day bias in testing drug-induced QT prolongation may lead to mis judgment of patient risk. Drug developers must address the complication of adopting a circadian testing policy due to the significant interindividual variability in human circadian rhythms. [24, 25,28]

9. CONCLUSION

Chrono pharmacology plays a crucial role in improving drug efficacy and minimizing side effects by aligning medication administration with the body's biological rhythms. Understanding circadian rhythms and biological clocks helps optimize drug delivery systems, such as pulsatile drug delivery systems, ensuring drugs are administered at the right time for maximum therapeutic benefit. Advancements in Chrono pharmacology pave the way for more personalized treatments, enhancing patient compliance and outcomes in managing chronic diseases like cardiovascular disorders, cancer, and diabetes. The study underscores the importance of considering time-based drug administration in modern pharmacotherapy to improve healthcare practices and patient quality of life.

AUTHOR CONTRIBUTIONS

All authors are contributed equally.

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The authors have no conflicts of interest to declare.

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