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CHRONOTHERAPY- A NEW VISTA IN NOVEL DRUG DELIVERY: An Overview

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ABSTRACT

Chronotherapy is useful in the treatment of disease, in which drug availability is timed to match rhythms of disease, in order to optimize therapeutic effect and minimize side effects. The specific time that patients take their medication is very important as it has significant impact on success of treatment. If symptoms of a disease display circadian variation, drug release should also vary over time. Drug pharmacokinetics can also be time dependent; therefore, variations both in a disease state and in drug plasma concentration need to be taken into consideration in developing drug delivery systems intended for the treatment of disease with adequate dose at appropriate time.

KEY WORDS

Cicardian rhythm, Chronotherapeutics, Chronopharmacology, chronotherapeutic drug delivery system.

INTRODUCTION

In order to increase the effectiveness of drug there are many approaches have been applied, here one of the technique is described which chronotherapeutic drug delivery system is. Many functions of the human body vary considerably in a day. These variations cause changes both in disease state and in plasma drug concentrations. Human circadian rhythm is based on sleep activity cycle, is influenced by our genetic makeup and hence, affects the body's functions day and night (24-hour period).[1] The dependence of bodily functions in certain disease states on circadian rhythm is well known. A number of hormones are released by the brain in the morning, while others are released during sleep. Blood pressure and heart rate are highest during the hours of 6.00 a.m. to 12.00 noon. [2]

To introduce the concept of chronopharmaceutics, it is important to define the concepts of Chronobiology and pharmaceutics. Chronobiology is the study of biological rhythms and their mechanisms. The term ''circadian'' was coined by Franz Halberg from the Latin circa, meaning about, and dies, meaning day. Oscillations of shorter duration are termed ''ultradian'' (more than one cycle per24 h). Oscillations that are longer than 24 h are ''infradian'' (less than one cycle per 24 h)rhythms. Ultradian, circadian, and infradian rhythms coexist at all levels of biologic organization.[3] Pharmaceutics is an area of biomedical and pharmaceutical sciences that deals with the design and evaluation of pharmaceutical dosage forms (or drug delivery systems) to assure their safety, effectiveness, quality and reliability .

Chronotherapeutics

The first chronotherapy to be widely applied in clinical practice was introduced in the 1960s — the alternate-day morning schedule of conventional tablet corticosteroid medication . Other chronotherapies have since been widely used in clinical medicine in the U S, Europe , and

Asia ; these include special evening theophylline systems for chronic obstructive pulmonary disease , conventional evening H2-receptor antagonists for peptic ulcer disease , and conventional evening cholesterol medications for hyperlipidemia .

Chronopharmacology and chronotherapeutics are the two scientific domains that study specifically when drugs produce their best effectiveness and least side effects.

The term "chrono" basically refers to the observation that every metabolic event undergoes rhythmic changes in time. Researchers have concluded that all living organisms are composites of rhythms with varying frequencies that may range from seconds to seasons. Perhaps the best known and studied chronobiologic frequency is the circadian rhythm which approximates the earth's 24-hour rotation around the sun. [4] Researchers have recently concluded that both disease states and drug therapy are affected by a multitude of rhythmic changes that occur within the human body[5]

Chronotherapeutics refers to a treatment method in which in vivo drug availability is timed to match rhythms of disease in order to optimize therapeutic outcomes and minimize side effects. It is based on the observation that there is an interdependent relationship between the peak to trough rhythmic activity in disease symptoms and risk factors, pharmacologic sensitivity, and pharmacokinetics of many drugs.[6]

The tradition of prescribing medication at evenly spaced time intervals throughout the day, is an attempt to maintain constant drug levels throughout a 24-hour period, may be changing as researchers' report that some medications may work better if their administration is coordinated with day-night patterns and biological rhythms.[7]

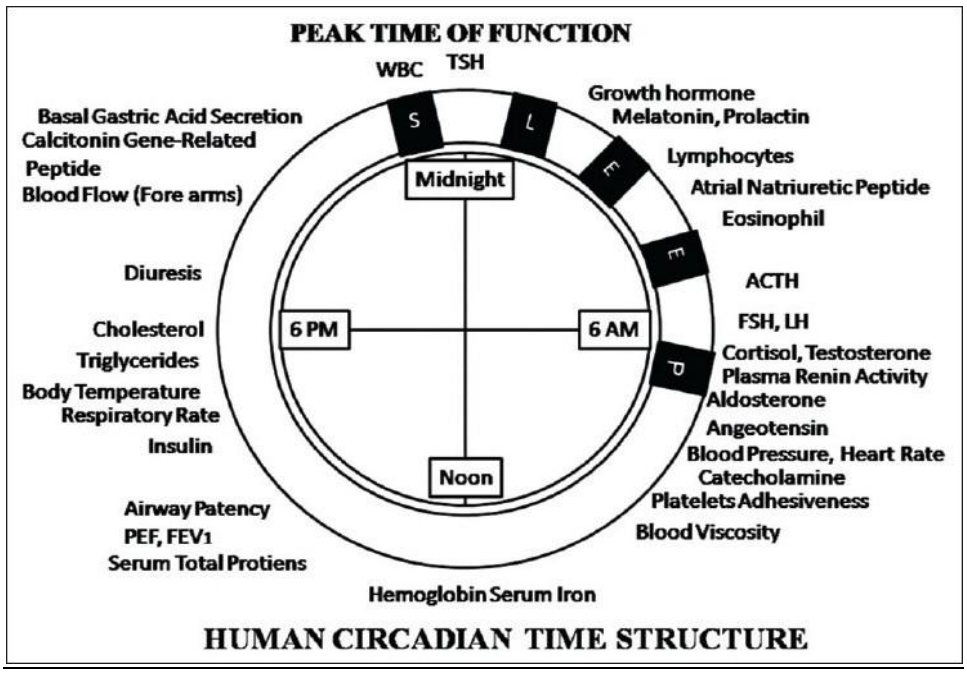

Fig. 1 Circadian time structure

(The term “circadian” derives from the Latin phrase “circa diem,” which means “about a day.”)

The biological rhythm studies help in defining the temporal organization of human beings. One means of illustrating the human circadian time structure is to depict the peak time of 24-h rhythms on a clock Shown is the approximate peak time of circadian (24-h) rhythms of selected biological variables in persons adhering to a normal routine of daytime activity (6–7 a.m. to 10–11 p.m.) alternating with nighttime sleep. For example ,the Circadian rhythms in the blood level of adrenocortical tropic hormone (ACTH), follicle stimulating hormone (FSH), luteinizing hormone (LH), testosterone, cortisol, catecholamines, renin activity, aldosterone, and angiotensin peak near the end of nighttime sleep or start of daytime activity. The morning peak of the rhythm in vaso-active entities contributes to the morning peak time of the circadian rhythms in heart rate, blood pressure, arterial compliance, and vascular resistance in normotensive and uncomplicated essential hypertension persons, and the morning peak of the circadian rhythm in blood catecholamines gives rise to the morning peak of the circadian rhythm in platelet aggregation.The activity in light and sleep in darkness in a daily routine determines the phasing of all circadian rhythms. Together, the phasing (peak time) of these and numerous other 24-h rhythms in biological processes and functions make up the circadian time structure of human beings, giving rise to day–night patterns in disease activity, with the potential for varying-in-time requirements for pharmacotherapy, as well as administration-time differences in the kinetics and dynamics of medications.

Molecular Mechanisms of biological timekeeping

Daylight with a high blue component has an activating effect. It stimulates the receptors in the eye and therefore the control center in the brain to a much greater extent than light with a high red component. Light acts via the photoreceptors in the eye on the control center in the brain. These photoreceptors are very evenly distributed over the retina. The signal to the brain and therefore the biological effect is greatest when as many photoreceptors as possible are stimulated simultaneously. Indirect lighting in which light is reflected from a large bright surface therefore has a stronger impact than the concentrated light from a spotlight.

The key breakthrough in understanding the circadian system was discovery of the molecular mechanisms of the circadian clock (“molecular clock”). Molecular mechanisms underlying circadian rhythms are conceived as a series of interlocking molecular loops, involving rhythmic transcription of specific “clock genes”, and interactions of the proteins they encode. In a simplified model, these clock genes comprise “positive elements” such as clock and Bmail1, whose protein products dimerize, enter the nucleus, and stimulate transcription of negative elements period 1, 2, and 3 (Per 1-3) and cryptochrome (Cry 1-2). The protein products of these genes (*per* 1-3, cry 1-2) in turn oligomerize, enter the nucleus, and suppress the activity of the clock/Bmail1 complex.[8] .These circadian rhythms are controlled by an inherited master clock network composed of the paired supra chiasmatic nuclei (SCN) which are situated in the ventro-rostral part of the hypothalamus function as the master pacemaker of an endogenous circadian timekeeping system.[9]. In mammals, the paired suprachiasmatic nuclei (SCN) located in The SCN receive photic input from the retina via direct and indirect pathways, thus forming the prime relay between external and internal times. The SCN synchronises the periphery via humoral and neuronal pathways and via the regulation of activity, nutrient uptake and body temperature by means of transcriptional control

of ccgs peripheral oscillators translate time information into physiologically relevant signals. Perturbations of the circadian system have a profound impact on health and wellbeing. The physiological and psychological disturbances following trans-meridian travel (*jet lag*) are rooted in a transient state of internal de-synchronisation while the body's clocks struggle to adapt to an abruptly shifted external light/dark cycle.

In recent years, multiple molecular feedback loops (molecular clock machinery) were identified, which further fine-tune generation of intracellular circadian rhythms. A number of important nuclear receptors such as REV-ERB, ROR or PPAR, interact closely with circadian feedback loops. The regulation of clock genes, by nuclear receptors, renders the clock responsive to numerous circulating hormones (*e.g.* cortisol, estrogen), nutrients signals (*e.g.* fatty acids derivatives) and cellular redox status (NADH/NAD+ratio). Nuclear receptors are now recognized as key intermediaries between the molecular clock machinery and a wide array of physiological processes [8]. Biological timekeeping is an evolutional adaptation to an environment that is organized in time, displaying discrete and important cyclic phenomena. Thus, the temporal organization of biological processes and functions during the 24-h period ensures peak functioning of the diurnal human species during daytime activity and restoration and repair during nocturnal rest; during the menstrual cycle, it ensures fertility and perpetration of the species; and during the year it ensures a priori biological adjustment to predictable-in-time changes and challenges associated with the different seasons of the year.

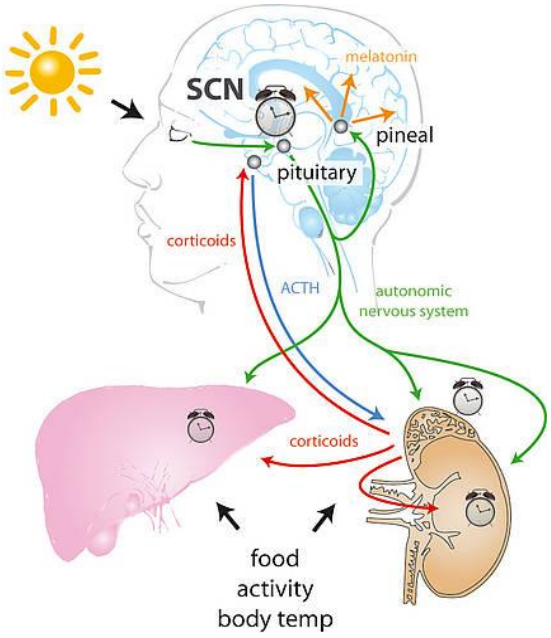

Fig. 2 supra chiasmatic nuclei (SCN) controlling circadian rhythm.

BIOLOGICAL MARKERS

The classic phase markers for measuring the timing of a mammal's circadian rhythm are:

1. Core body temperature-

For temperature studies, subjects must remain awake but calm and semi-reclined in near

darkness while their rectal temperatures are taken continuously. The average human adult's temperature reaches its minimum at about 05:00 (5 a.m.), about two hours before habitual wake time, though variation is great among normal chronotypes[10]

2. Plasma level of cortisol-A third marker of the human pacemaker is the timing of the maximum plasma cortisol level. Klerman in 2002 compared cortisol and temperature data to eight different analysis methods of plasma melatonin data, and found that "methods using plasma melatonin data may be considered more reliable than methods using CBT or cortisol data as an indicator of circadian phase in humans. [11]

3. Melatonin secretion by the pineal gland:

Melatonin is absent from the system or undetectably low during daytime. Its onset in dim light, *dim-light melatonin onset* (DLMO), at about 21:00 (9 p.m.) can be measured in the blood or the saliva. Its major metabolite can also be measured in morning urine. Both DLMO and the midpoint (in time) of the presence of the hormone in the blood or saliva have been used as circadian markers. However, newer research indicates that the melatonin *offset* may be the more reliable marker. Benloucif et al. in Chicago in 2005 found that melatonin phase markers were more stable and more highly correlated with the timing of sleep than the core temperature minimum. They found that both sleep offset and melatonin offset were more strongly correlated with the various phase markers than sleep onset. In addition, the declining phase of the melatonin levels was more reliable and stable than the termination of melatonin synthesis.[10]

One method used for measuring melatonin offset is to analyze a sequence of urine samples throughout the morning for the presence of the melatonin metabolite 6-sulphatoxymelatonin (aMT6s). Laberge in Quebec in 1997 used this method in a study that confirmed the frequently found delayed circadian phase in healthy adolescents. [12]

The regulator for our internal clock

Biorhythms dictate when we wake up, when we become tired and when we fall; they even have an effect on our body temperature and much more. This internal clock is influenced to a large extent by light. Although our genetic makeup determines our circadian rhythm, this rhythm has to be resynchronized by daylight each and every day. If light, the most important zeitgeber, is lacking then our internal clock soon goes out of sync. As a result we may suffer from sleep disorders, chronic fatigue and in the worst case clinical depression.

- **Circadian rhythm hormone secretion**

  The hormones responsible for the circadian rhythm in humans are **melatonin**, which is released in response to increasing levels of darkness and which promotes sleep and **cortisol** which is the biological opposite of melatonin and an indicator of the level of human activeness.

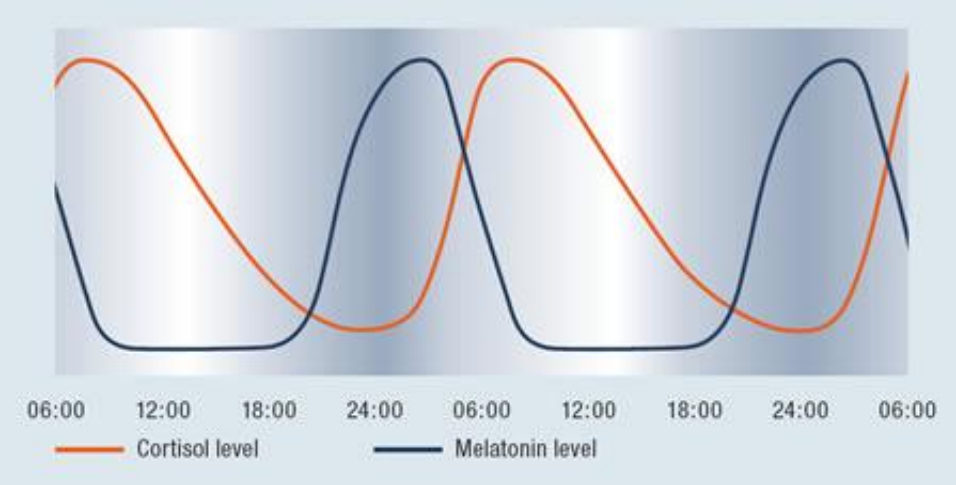

Fig. 3 Effect of light on secretion of harmones.

Molecular Genetics of Circadian Rhythms

As discussed previously, the properties of circadian clocks suggested cyclic changes in the expression of certain genes as a possible mechanism underlying the internal pacemaker. This hypothesis was supported by the demonstration in a number of species that the expression of genes and the production of proteins encoded by those genes were required for normal clock function. Nevertheless, a completely different experimental approach ultimately led to the identification of molecular circadian clock components. Researchers used chemical agents to introduce numerous, random mutations into the DNAs of the fruit fly, *Drosophila melanogaster,*[13] and of the filamentous fungus *Neurospora*. The resulting mutant organisms then were screened for rhythm abnormalities. This mutagenesis approach led to the identification of the first circadian clock mutants, which were called *period* (*per*) and *frequency* (*frq*, pronounced "freak"). The genes that carried the mutations in these organisms were cloned in the 1980s [14]. However, considerable frustration ensued as researchers sought to isolate the equivalent genes in mammals (i.e., mammalian homologs). Finally, in the early 1990s, researchers began a similar mutagenesis screening approach in the mouse and described the first mouse circadian mutation, called *Clock,* in 1994 . In 1997 the gene affected by this mutation became the first mammalian circadian clock gene to be cloned [14]. Like the mutants of the *Per* and *Frq* genes, the altered *Clock* gene both affected the free-running rhythm period (i.e., lengthened the period) and caused a loss of persistence of circadian rhythms under constant environmental conditions. Both the C*lock* mutant in mice and the *Per* mutant in flies were the first animals of their respective species identified using such a mutagenesis approach in which the mutation manifested as altered behavior rather than an altered physiological process.

Since the discovery of the *Clock* gene in mice, the list of circadian clock genes identified in mammals has grown in a remarkably short period of time. For example, researchers have identified not one, but three mammalian genes that correspond to the per gene in both their structure (i.e., nucleotide sequence) and their function [14]. Some of the pro-posed circadian clock genes have been identified solely based on their similarity in sequence to *Drosophila* clock genes and have not been confirmed to have clock function based on an examination of the

behavior of the corresponding mutants. Nevertheless, the findings to date clearly indicate the outline of a pacemaker that is based on a feedback cycle of gene expression.

Basic Types of chronotherapy

Bright Light Therapy

The administration of correctly timed, properly dosed, high-intensity fluorescent light to treat various forms of depression. [15]

Wake Therapy (Sleep Restriction)

The use of prolonged periods of wakefulness, with intervening periods of recovery sleep, to induce rapid improvement in depressive symptoms.[16][17]

Sleep Phase Advance

Moves the time of sleep forward to the early evening to potentiate the action of other antidepressant interventions.[18]

Triple Chronotherapy

The combined use of Wake and bright light therapies along with sleep phase advance to generate a fast and sustained antidepressant response. [15-18]

Dawn Simulation

Use of a progressive illumination signal, administered during the end of sleep, to treat Seasonal Affective Disorder. [19]

Chronobiotics

Circadian rhythm-modifying compounds such as melatonin and certain psychiatric medications that treat depression and sleep disorders. [20, 21]

Interpersonal Social Rhythm Therapy

A problem-solving therapy that increases the routine of one's everyday activities to improve mood stability in bipolar disorder.[22,23]

Theoretical and formal approaches to chronopharmaceutics

When treating human diseases, the overall goal is to cure or manage the disease while minimizing the negative impact of side effects associated with therapy. In this respect, chronopharmaceutics will be a clinically relevant and reliable discipline if pharmaceutical scientists could delineate(describe) a formal and systematic approach to design and evaluate drug delivery system that matches the biological requirement. The key component for the success of ChrDDS design for the treatment of diseases is the elucidation of control-relevant models for drug delivery.

A control-relevant model is the one that has:

(i) Predictive capability in terms of the process input – output behavior.

(ii) Utility in performing on-line calculations for control or optimization purposes. Because of the complexity of identified biological oscillators, two physical descriptors have been discussed to illustrate the mathematical description of such system: the linear mass -spring oscillator and the non-linear electrical oscillator described by vanderPol . The latter provides a simple example of an oscillator in which the variation of one parameter alters the system from being relatively insensitive to noise to one that is very sensitive.

(iii) A general introduction to the mathematics of biological oscillators can be found in the monograph by Pavlidis .

A number of modeling approaches are available in the broad area of hemodynamic variable regulation, cancer chemotherapy, and glucose concentration control.

CONCLUSION

Advances in chronobiology and chronopharmocology has demonstrated the importance of biological rhythms in treatment of disease and this has led to a new approach to

the development of novel drug delivery system-ChrDDS (Chronotherapeutical Drug Delivery System).

The overall success of chronopharmaceutics will depend on the successful integration of knowledge from future advances in development timing, system biology and nanotechnology. The selection of the appropriate chronopharmaceutical technology should take into considerations the application range (e.g. targeted drugs of different physico-chemical properties), the ease of manufacturing, the cost-effectiveness, and the flexibility in the pharmacokinetic profile. By selecting optimal time to achieve the desired effect, treatment opportunities may arise and undesired side effects can be minimized.

As timing of drug administration in disease therapy has significant impact upon treatment success, optimal clinical outcome cannot be achieved if drug plasma concentrations are constant. If symptoms of a disease display circadian variation, drug release should also vary over time. ChrDDS in future is certainly going to gain popularity.

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