Review Article

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A Review Article on Chronotherapy

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ABSTRACT

Chronotherapy refers to the use of circadian, ultradian, infradian & seasonal or other rhythmic cycles in the application of therapy. There are number of conditions which show a circadian pattern and advantage could be taken by timing and adjusting the administration of drugs according to the circadian rhythm of the disease. Some of the conditions, which may be significantly benefited, are hypertension, myocardial infarction, bronchial asthma, peptic ulcer, arthritis, duodenal ulcer, diabetes, neurological disorder, cancer and hypercholesterolemia. Chronotherapy can be classified into time controlled systems wherein the drug release is controlled primarily by the delivery system, stimuli induced PDDS in which release is controlled by the stimuli, such as the pH or enzymes present in the intestinal tract or enzymes present in the drug delivery system and externally regulated system where release is programmed by external stimuli like magnetism, ultrasound, electrical effect and irradiation.

Keywords: Chronotherapy, Circadian Rhythm, Chrono pharmaceutics, Time Dependent Release, circadian clock, Chrono therapeutics.

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INTRODUCTION

Circadian rhythm regulates many body functions in humans, like metabolism, physiology, behaviour, sleep patterns, hormone production, etc. The release of some drugs is preferred in pulses i.e. the release of drug as a "pulse" after a lag time has to be designed in such a way that a complete and rapid drug release should follow the lag time. Lag time is defined as the time between when a dosage form is placed into an aqueous environment and the time at which the active ingredient begins to release from the dosage form. These systems are also called time-controlled as the drug released is independent of the environment[1] A single dosage form provides an initial dose of drug followed by one release-free interval, after which second dose of drug is released, which is followed by additional release-free interval and pulse of drug release[2]. Chrono pharmaceutics is a branch of pharmaceutics (science and technology of drug dosage forms) meant to the design and evaluation of drug delivery systems that release a bioactive agent at a rhythm that ideally matches in real time the biological requirement for a given disease therapy or prevention 'Chrono pharmaceutic Drug Delivery System' uses the basic concepts of human chronobiology and the rhythm dependence of certain disease states and the pharmacodynamics of medications. The drug therapy can be optimized by tailoring the dosing schedule based on chronobiological pattern. The safety and efficacy of the drug is achieved by coordinating the peak plasma concentration of the drug with circadian rhythm of the body[3].

A Brief History of Circadian Rhythm Knowledge:

Circadian rhythms in nature were observed for a long time, but their importance in physiology has come back into the spotlight recently. The circadian clock has gained much notoriety with the Nobel Prize in Physiology or Medicine awarded to Jeffrey Hall, Michael Rosbash, and Michael Young for their studies on the molecular mechanisms controlling the circadian rhythm (Figure 1) In the plant kingdom, Androgens made the first report on circadian rhythmicity in the 4th century BC with the sleep movements of Tamaricus indicus' leaves. This proved that an endogenous clock was able to impose a rhythm to processes, which could be discriminated from simple responses to daily stimuli [4-6].

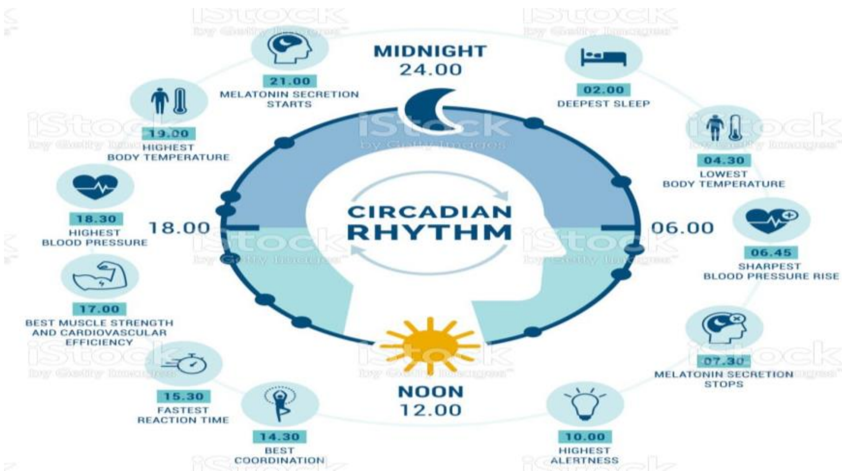

Figure 1: Circadian rhythm cycle:

Chrono therapeutics:

Chrono therapeutics is the discipline concerned with the delivery of drugs according to the intrinsic activities of a disease over a certain period of time because the biochemical, physiological and pathological variations over a 24h period in humans have occurred[7].

Different types of the rhythms affecting human body:

Ultradian: These are the cycles shorter than a day. E.g. 90 minutes sleep cycle.

Circadian: This lasts for over 24 hours. E.g. sleeping and waking patterns.

Infradian: Cycles longer than 24 hours. E.g. monthly menstruation.

Seasonal: Such as seasonal affective disorder (SAD), this causes depression during the short days of winter in susceptible people[8]. The shift from conventional sustained release approach to modern pulsatile delivery of drugs can be credited to the following reason(s):

First pass metabolism:

Some drugs, such as beta blockers, and salicylamide, undergo extensive first pass metabolism and require fast drug input to saturate metabolizing enzymes in order to minimize pre-systemic metabolism. Thus, a constant/sustained oral method of delivery would result in reduced oral bioavailability.

Biological tolerance:

Continuous release drug plasma profiles are often accompanied by a decline in the pharmacotherapeutic effect of the drug, e.g., biological tolerance of transdermal nitro glycerin.

Special chrono pharmacological needs:

Circadian rhythms in certain physiological functions are well established. It has been recognized that many symptoms and onset of disease occur during specific time periods of the 24hour day, e.g., asthma and angina pectoris attacks are most frequently in the morning hours.

Local therapeutic need:

For the treatment of local disorders such as inflammatory bowel disease, the delivery of compounds to the site of inflammation with no loss due to absorption in the small intestine is highly desirable to achieve the therapeutic effect and to minimize side effects.

Gastric irritation or drug instability in gastric fluid:

For compounds with gastric irritation or chemical instability in gastric fluid, the use of a sustained release preparation may exacerbate gastric irritation and chemical instability in gastric fluid.

Drug absorption differences in various gastrointestinal segments:

In general, drug absorption is moderately slow in the stomach, rapid in the small intestine, and sharply declining in the large intestine. Compensation for changing absorption characteristics in the gastrointestinal tract may be important for some drugs. For example, it is rational for a delivery system to pump out the drug much faster when the system reaches the distal segment of the intestine, to avoid the entombment of the drug in the faeces[9,10].

Advantages of Chronotherapy:

- Chronotherapy is drug-free.
- It is more effective when a person sleeps for several hours.
- While Chronotherapy patients often fall asleep this improves their condition and confidence as well.
- It is different from other treatments because it got the beginning, middle, and an end. So one can predict easily the point at which it will work.
- It gives a new schedule like getting up and sleeping early which will be quite unusual for some days but it will give a period to adjust psychologically[11].

Disadvantages of Chronotherapy:

- It develops a non 24 hours sleep wake syndrome after the treatment as the person sleeps for over 24 hours during the treatment. It’s not quite common but the degree of risk is not known.
- Person may also be deprived of sleep sometimes.
- Person become less productive during chronotherapy and staying awake till the other schedule might be bit uncomfortable.
- Person will have to take some time off from your busy normal schedule as its time taking therapy.

- Person has to keep himself awake till the next sleep schedule so he have to get himself busy so that he stay awake till the other schedule.
- Medical supervision is mandatory for this therapy and regular consulting of sleep specialists is recommended.
- Person undergoing therapy may feel unusually hot or cold sometimes[11].

FREQUENCY OF BIOLOGICAL RHYTHM:

Biological rhythms are repetitive biological processes ranging in frequency from more than once per second to less than once every decade. Some biological rhythms are mere responses to environmental cycles, while others are endogenously generated and may additionally respond to environmental cycles. Most research on biological rhythms conducted during the past 50 years has dealt with daily and annual rhythms and has concentrated on basic behavioral, physiological, neural, and molecular processes studied in a small number of species in the laboratory. Few studies have examined interspecies differences in basic processes or have addressed ecological issues in natural environments. Perhaps the most fundamental ecological issue dealing with daily (circadian) rhythms is an organism's adoption of a nocturnal niche or a diurnal niche. Although many organisms today can be classified as either nocturnal (night-active) or diurnal (day-active), many others defy classification. There seems to be a gradient of temporal niches running from predominantly diurnal species to predominantly nocturnal species with many chronotypes in between, including species exhibiting wide inter-individual gradients of temporal niche. Very little is known about the causes of temporal niche selection beyond the obvious fact that some species inherit a diurnal preference while others inherit a nocturnal preference or no preference at all.

Table 1: Frequency range in biological rhythm

Domain	Range
Ultradian	$t<20$ h
Circadian	$20h \leq t \leq 28h$
Infradian	$t>28h$
Circaseptam	$t=7\pm$ 3days
Circadiseptan	$t=14\pm$ 3days
Circaviginatan	$t=21\pm$ 3days
Circatriginatan	$t=30\pm$ 3days
Circannual	$t=1$year$\pm$3months

(**Source:** Piccione and Caola, [5])

CHRONOTHERAPY IN VARIOUS DISEASES:

Asthma:

It is characterized by airway inflammation resulting in hyper responsiveness of lower respiratory tract to various environmental stimuli. Airway resistance increases progressively at night in the patient. Asthma is the most common disease in which the large circadian variation occurs with respect to time. There is an increased incidence of asthma during the early-morning hours. The symptoms of asthma occur 50 to 100 times more at night. The exacerbation of asthma during the night represents the changing status of biological functioning due to circadian rhythms in bronchial patency; airways hyper reactivity to acetylcholine, histamine, and house dust; and plasma cortisol, epinephrine, histamine, and cyclic AMP. Once daily dosing of inhaled glucocortico steroid cyclesonide, sustained release theophylline, transdermal tulobuterol patch found to be effective in case of nocturnal asthma [12].

Cardiovascular disease:

In cardiovascular disease capillary resistance and vascular reactivity are higher in the morning and decreases later in the day. Increased platelet aggregation and decreased fibrinolytic activity in the morning leads to relative hypercoagulability of the blood. Also BP is at its lowest during the sleep cycle and rises steeply during the early morning awakening period. These observations shows that myocardial ischemia, angina pectoris, acute myocardial infarction, congestive cardiac failure and sudden cardiac death are also unevenly distributed during the 24 h with greater expected events during the initial hours of the daily activity span, in the late afternoon or early evening. Both sympathetic activity and the Renin – angiotensin - aldosterone axis peak in the early morning hours. External factors affecting ANS including physical activity, emotional state, meal and sleep/wake routine also contribute to variations. Currently, there are chronotherapeutic antihypertensive products like oral nitrates, calcium channel blocker and β-adrenoceptor antagonist whose both pharmacokinetics and pharmacodynamics get influenced by circadian rhythm are available with novel drug delivery systems, releasing drug during the vulnerable period of 6 am to noon upon administration of medications at 10 pm [13].

Cancer:

Human and animal studies suggest that chemotherapy may be more effective and less toxic if cancer drugs are administered carefully at selected times that take advantage of tumour cell cycles while less toxic to normal tissue. The rhythmic circadian changes in tumour blood flow and cancer growth are relevant both when tumours are small and growing most rapidly and when they are larger and growing more slowly. Circadian chemotherapy timing meaningfully affects drug toxicity patterns and severity, maximum tolerated dose, average dose intensity, tumour response quality and frequency and the survival of patients with cancer. The cancer chrono genetic therapy found to be effective in tumour suppression in vivo. For example, it has been shown that CLOCK genes dictate sensitivity to the anticancer drug cyclophosphamide [14].

Peptic ulcer:

Many of the functions of the gastrointestinal tract are subject to circadian rhythms: gastric acid secretion is highest at night. While gastric, small bowel motility and gastric emptying are all slower at night. Suppression of nocturnal acid is an important factor in duodenal ulcer healing. Therefore, for active duodenal ulcer, once daily at bedtime is the recommended dosage regimen for H2 antagonists. Bedtime H2-receptor blockade using Chronotherapy overcome problems of sustained or profound decrease of 24-h intragastric acidity including the threat of enteric infection and infestation, potential bacterial overgrowth with possible N-nitrosamine formation[15].

Arthritis:

Rheumatoid arthritis can be distinguished from osteoarthritis by the time of day when the patient's joints are most painful and morning stiffness is characteristic feature of rheumatoid arthritis whereas symptoms are often worse in the afternoon and worse in evening in osteoarthritis. Non-steroidal anti-inflammatory drugs are taken for relieving the morning pain and stiffness of rheumatoid arthritis so the medicines are taken late at night and it is better for the treatment. Chronotherapy for all forms of arthritis uses standard treatment that includes the non-steroidal anti-inflammatory drugs and corticosteroids but in the treatment the dosages time are match with the rhythms of disease which are timed to ensuring that the highest blood levels of the drug coincide with peak pain.

Hypercholesterolemia:

The higher rates of cholesterol intake during the hypercholesterolemia and hepatic cholesterol genesis occur during the evening hours even in the fasting state also. The free cholesterol levels have been reported to be lowest at 2 p.m. to 6 p.m. and peak at 6 am and morning versus evening administration of HMG-CoA reductase antagonists [16].

Allergic Rhinitis:

Symptoms of allergic rhinitis (e.g. nasal congestion, sneezing, running nose) are typically more severe in the early-morning hours. If the administration of the drug can be matched with the biological time structure which have the peak with the biological time structure which have the peak pharmacologic activity are matching the time of greatest discomfort, optimum relief may be provided at the time when it is needed most of the patient.

Mood Disorders:

The deprivation of sleep in the half of the night and the timed exposure to day light-intensity and artificial light still experimental therapies, may ease the depression pre menstrua or during menopause and benefit both women and men with seasonal and other mood disorders. Such a variation was not detected in the mood disorders when sustained release dosage forms of nifedipine and isosorbide mononitrate were used.

Diabetes:

In type I diabetes the circadian rhythms of insulin and its action are of physiological interest and clinical importance. So, insulin is released in pulsatile fashion but sometimes it is irregular. Insulin can show its cyclic rhythmicity of 8-30 min which can show the optimal action. The modulators of insulin release and action are secreted in a circadian pattern and impress the mode of insulin release. So difference between maximum and minimum plasma insulin concentration has short-term rhythmicity and complex secondary circadian rhythm is variable early-morning and late-afternoon insulin resistance.

Sleep disorders:

Many biological signals like sleep disorder occurring in the central and autonomous nervous systems this shows the complex time structure with rhythmic and pulsatile variations in multiple frequencies. Sleep mainly consists of a rhythmic combination or circadian changes in physiological, biochemical and psychological processes. The circadian rhythm disturbances also differ from person to person and identification of the individual variation would be important in dealing with certain sleep disorders.

Epilepsy:

The circadian rhythm also plays a significant role in seizures of epilepsy. The influence of the biological clock on seizure of some partial seizures has been found in animals or humans. The behavioural chronobiology provides the detection of new regulation processes that concerns central mechanisms of epilepsy because the circadian psycho physiological patterns of epilepsy show dynamic biological systems which show some inter modulating endogenous processes between observation and seizure susceptibility. Such chronobiologic studies applied to epileptic behaviour and this suggests the development of new heuristic aspects in the field of comparative psychophysiology.

Alzheimer’s disease:

The change of circadian rhythm is also seen in patients with Alzheimer's disease. Individuals with Alzheimer's symptoms show less diurnal motor activity and higher percentage of nocturnal activity which show the lower inter daily stability of motor activity and activity of macrophages peak time than normal healthy individuals. The core body temperature is also higher in patients and the circadian abnormalities are seen together with cognitive and functional deterioration in this disease.

Parkinson's Disease:

Parkinson's disease discloses many alterations in circadian rhythm of blood pressure; amplified diurnal blood pressure variability and postprandial hypotension are due to autonomic dysfunction. But existence of circadian rhythm in this disease has not been evaluated in clinical data because the daily fluctuations of motor activity pattern of the phase of the disease and the subsequent role of drugs are difficult to estimate[17].

Chronotherapy in COPD:

COPD is a slowly progressing asymptomatic disease of the lungs which causes irreversible expiratory airway issues. The induction of inflammatory processes in the lungs via cigarette smoking or toxic gases causes decreased elasticity of the alveolar passage, resulting in limited airway space. This narrows the space of the bronchial tree, causing emphysema, and in turn leading to hyperinflation. In addition, hypoxemia develops in the latter stages of COPD, which causes the diaphragm to flatten and ribs to enlarge.

The response of patients to a certain formulation in terms of efficacy and acceptability is based on biological timing and endogenous periodicities. The principal action of chronotherapy is based on receptor–ligand interactions that cause the activation of downstream intracellular signalling pathways, the stimulation of effector molecules and increased production of secondary messengers, along with diurnal variations. This therapy also increases the efficiency of modern therapeutic drugs which are dependent on a number of factors, such as controlled drug release or chrono-modulated drug delivery corresponding with the disease rhythm and drug adsorption, targeting the physiological system via chromodynamics and chronotoxicology. The primary therapeutic treatment for COPD includes long-acting inhaled bronchodilators (LAMAs or LABAs). In the case that disease control is not achieved via LAMAs or LABAs, the guidelines then suggest a combination of two treatments. Although there is widespread agreement on the benefits of LAMAs and LABAs in the treatment of COPD, the position of inhaled glucocorticoids in this treatment has been a matter of debate due to their lack of efficacy, safety concerns, and the risk associated with pneumonia. The administration of an inhaled glucocorticoid should be confined to patients with significant loss of lung function and frequent exacerbations based on the guidelines of the Global Initiative for Chronic Obstructive Lung Disease (GOLD).

Chronotherapy in COVID-19:

The COVID-19 pandemic means that the discovery of safe and effective therapies for SARS-CoV-2 is urgently needed. The understanding of chronobiology with regard to how COVID-19 infection affects circadian rhythms may provide opportunities for the development of chronotherapy for SARS-CoV-2. The host immune responses in COVID-19, particularly the severe inflammation that can possibly cause multi-organ failure, strongly modulate disease severity. The activity of all components of the immune system, including the inflammatory immune responses, follow robust CR. It is predicted that the severity of COVID-19 infection depends on the time (day or night) when infection occurs, because the harm caused by a rapidly replicating virus and the way it is offset by our immune system depends on the phase of the circadian rhythm of the host. This can be confirmed by both in vitro and in vivo experimental setups where human cell lines (in vitro) and mouse models (in vivo) are infected with SARS-CoV-2 in both the active phase and resting phase (12 h apart).

In COVID-19 cases, a group of patients experience cytokines release storm (CRS) that results in acute respiratory distress syndrome (ARDS). Since the intrinsic circadian clock of the lungs, together with the immune system, regulate the various component of CRS, the use of chrono-targeted therapy can be very effective in the management of ADRS during COVID-19 infection. As there is variation in the circadian rhythm in lungs and the immune system (between healthy and diseased), the effect of immune metabolic modulators or anti-inflammatory drugs on cells or cytokines release from diseased cells/tissues also depends on the timing of administration .It is likely that the appropriate selection of anti-inflammatory chronotherapy can be beneficial to combat the detrimental CRS and ADRS during COVID-19 infections. For example, chronotherapy can differentially alter the level of different cytokines such as chemokine (C-X-C motif) ligands (CXCL10), IL-1β, IL-4, IL-8, IL-10, TNFα and Toll-like receptors during viral infection, including COVID-19. Following this observation, a recent investigation on a murine bone injury (tibia fracture) model showed that anti-inflammatory cytokines such as IL-13 and IL-4 and clock genes such as *Per2* could be effectively regulated by administrating non-steroidal anti-inflammatory drugs during the active phase of the circadian rhythm. Interestingly, the cytokines that were modulated by the timing of drug administration coincide with cytokines such as IL-1β, IL-8, IL-10R, IL-6R and TNFα that are involved in the CRS in COVID 19.

Enhancing Circadian Rhythms to Improve Health

Circadian rhythms can be enhanced through non-invasive interventions such as bright light or scheduled meal times, making them an ideal target for improving basic health and fitness, in other words, preventive medicine.

Chrono-Phototherapy:

Light is the most well-established means to entrain circadian rhythms, although no specific treatment or light device is FDA approved. Morning bright light exposure, has been widely touted as a way to treat sleep disorders (e.g. advanced or delayed sleep phase syndromes), neuropsychiatric disorders (e.g. autism spectrum disorder, attention deficit hyperactivity disorder, seasonal affective disorder, dementia), associated with genetically, environmentally, and pathologically perturbed circadian rhythms. Randomized, double-blind, parallel-arm, placebo-controlled studies showed that light therapy improves mood and insulin sensitivity in patients with major depression and type 2 diabetes Concomitantly, bright light therapy is emerging as a chronotherapeutic tool to alleviate motor disorders, sleep/wake alterations, anxiety, and depression in patients with neurodegenerative disease. Light also regulates melatonin levels, and some studies show that melatonin inhibits the growth of tumours. Although melatonin is suppressed by light, daytime blue light enhances the effect of nighttime melatonin in inhibiting the growth of prostate, liver, and breast cancers. These correlate with previous reports that melatonin depletion by light exposure late at night stimulates the growth of multiple human cancer xenografts, increasing drug resistance. Other experimental human studies with a simulated night shift model show that bright light induces complete and rapid adjustment of peripheral clocks, suggesting phototherapy as a potential non-pharmacological intervention to counteract the deleterious effects of shift work or jet lag. Overall, these studies suggest that targeting the neuro-hormonal axis with light could have benefits in disease prevention and treatment [21].

Chrono-Diet:

Restricting food intake to a specific daily interval synchronizes some peripheral clocks and has become a popular way to improve metabolic health. The health benefits of clock-modulating diets have been increasingly recognized as has the dynamic cross-talk between circadian clocks and metabolic pathways. The molecular circadian clock directly or indirectly synchronizes diverse metabolic processes such as gluconeogenesis, mitochondrial metabolism, and lipogenesis. This involves circadian regulation of uptake, synthesis, and break-down of nutrients (e.g; glucose, amino acids, lipids) via rhythmically controlled expression and activity of transporters or enzymes. Reciprocally, the clock receives input from nutrient signalling pathways (e.g; NAD +-dependent), which function as rheostats to coordinate metabolic processes with daily cycles of sleep/wake and fasting/feeding.

Clock-enhancing diets and aging

TRF and other dietary interventions have the potential to counteract aging via circadian rhythm enhancement. A fly model revealed that TRF attenuates age-related cardiac decline in

Drosophila. Moreover, short-term intermittent fasting in young flies extended lifespan by improving gut health and resistance to oxidative stress. Interestingly, even caloric restriction (CR), which is a well-known lifespan-extending dietary intervention, improves circadian cycling in flies.

In mice as in flies, circadian molecular and metabolic profiles altered by aging are reversed by CR. Solanas and colleagues showed that age-associated rewiring of the oscillatory diurnal transcriptome in adult stem cells, such as the switch from genes involved in homeostasis to those involved in tissue-specific stresses (e.g. DNA damage, inefficient autophagy), was prevented by long-term CR. In a parallel study, CR rescued the aging-dependent decline in the global rhythms of transcription and protein acetylation in the liver, improved NAD + availability, enhanced SIRT1 activity, and increased levels of acetate and acetyl-co A, all indicative of enhanced longevity

Clock-enhancing diets and cancer

In addition to anti-aging benefits, preclinical evidence indicates that CR may have anticancer effects by reducing tumor progression, enhancing the death of cancer cells, and increasing the effectiveness and tolerability of chemo and radiotherapies. Nonetheless, it is increasingly recognized that chronic CR often has detrimental effects on tumor development and chemotherapy, possibly by negatively affecting the immune system, wound healing, and other important functions. Instead, intermittent fasting (IF), a diet-based therapy that alternates between fasting and free feeding/eating for a period of time, reportedly inhibits tumor growth and improves antitumor immune responses in preclinical and clinical studies. Furthermore, IF can increase cancer sensitivity to chemotherapy and radiotherapy and reduce the side effects of traditional anticancer treatments. Together these findings holds promise for well-designed dietary intervention tailored to the host’s circadian rhythms as a potential therapeutic regimen to counter cancer.

Chrono-exercise and aging:

As with TRF, exercise is gaining attention as a potential chrono-therapeutic intervention in the prevention and treatment of multiple diseases. In earlier animal studies, exercise was shown to have positive health effects by strengthening circadian rhythms. For example, Schroeder and colleagues showed that scheduled exercise during the late-night improved many of the rhythmic deficits, including gene expression changes, observed in mice deficient in the peptide vasoactive intestinal polypeptide. Furthermore, aged mice housed with a running wheel showed stronger circadian rhythms in locomotor activity, faster recovery of internal synchrony following a phase advance of 8 h, and increased amplitude of the firing rate rhythm in the SCN, when compared to aged mice housed without a running wheel. Together with clinical evidence on the protective effect of exercise against multiple morbidities, particularly associated with aging, these results provide a rationale for scheduled exercise as a potential tool to counteract genetic, environmental, and pathophysiological disruptions of circadian rhythms [22].

Chrono-exercise and metabolic health:

Skeletal muscle has an intrinsic circadian clock that is critical for regulating metabolic activity. Indeed, multiple metabolic indices in the muscle, such as glucose tolerance, insulin sensitivity, and muscle oxidative capacity, show circadian oscillations and these are influenced by the timing of exercise. Showed that both mice and humans exhibit differences in exercise capacity between the early and late part of their active phase, with exercise inducing a time-of-day-dependent transcriptomic and metabolic pattern in the mouse skeletal muscle. ZMP, an endogenous AMPK activator, is induced by exercise in a time-dependent manner to regulate key steps in glycolytic and fatty acid oxidation pathways, which may in turn enhance exercise capacity Sato and colleagues showed that exercise in the evening (beginning of active phase), rather than in the morning (beginning of rest phase), resulted in higher utilization of carbohydrates and ketone bodies, together with degradation of lipids and amino acids in mice. Exercise selectively activated HIF1α, a central regulator of glycolysis during hypoxia, in a time-dependent manner[23].

CHRONO CHEMOTHERAPY:

Host-tissue tolerance may vary with time of the day:

The earliest examples of chronotherapy are from the treatment of cancer, and circadian timing is now increasingly recognized as an important parameter to optimize therapy. Anti-cancer drugs are usually cytotoxic to normal tissues as well as malignant cells, so the goal is not just to improve efficacy but also reduce toxic side effects such as host tissue damage and immunological dysfunction. Timing cancer therapy may achieve an optimal balance between drug tolerance and efficacy. In earlier work, the efficacy of over 30 chemotherapy drugs was shown to vary by over 50% based on administration time. Some of the most commonly used anticancer drugs (e.g. cisplatin, doxorubicin, cyclophosphamide) exhibit differential toxicities depending on the time of administration. For example, chrono chemotherapy experiments with rat models for cancer found maximal benefit and minimal toxic effects when cisplatin was administered in the middle or later part of the active phase while doxorubicin was most effective when administered near the end of the daily resting phase .In patients with advanced ovarian cancer, administration of doxorubicin in the morning (e.g. 6 am) and cisplatin in the evening (e.g. at 1800 before or after doxorubicin) caused fewer complications and renal toxicity than administration of doxorubicin in the evening and cisplatin in the morning. Likewise, chronotherapy trials of patients with metastatic colorectal cancer showed that timed combination therapy with irinotecan, oxaliplatin, 5-fluorouracil (5-FU), and leucovorin resulted in delayed time to progression and increased overall survival with increased tolerance and safety, compared to routine chemotherapy[24].

Future Prospective:

Despite the considerable advancement in the field of circadian rhythms and chronotherapy, significant information-related gaps still exist between patients receiving treatment, community pharmacists and physicians based on prescription-related specifics, awareness of circadian rhythms, application, and attitudes toward the application of chronotherapy in practice. Therefore, physicians and community pharmacists could both play a key role in providing appropriate information to patients on optimal dosing times for effective clinical implementation and achieve maximum benefits of this therapy. Additionally, preliminary analysis and screening of newer drugs during preclinical studies for their chronotherapeutic potential could be an effective method to enhance research and development in pharmaceutical industries. Furthermore, elucidating molecular pathways that proceed with time-based worsening of symptoms and defining the role of the molecular clock in these pathways could provide a novel therapeutic target in future. In addition, chrono pharmacology (chrono pharmacokinetics and chrono pharmacodynamics) are other essential parameters that must be well-monitored and studied for adequate clinical responses. This knowledge may lead to the identification of biomarkers within circadian-expressed genes and can ultimately be used for the accurate estimation of drug administration timing in diseases.

CONCLUSION:

In the past ~25 years, extensive research in chronobiology has expanded our understanding of the functional role and mechanism of the circadian clockwork in human health and disease. Knowledge of the interactions across clocks in the body and between clocks and almost all physiological systems has not only elucidated circadian physiology and pathophysiology but also led to some successful therapeutic recommendations. Despite substantial progress in this area, several questions remain. (1) Are the therapeutic benefits of the extant small molecules targeting clock components mediated entirely by those components? Many drugs have multiple targets, so it is important to confirm that relevant effects are mediated by the clock molecule in question; this can be done by delivering the drug to cell or animals that lack that clock molecule. Using this approach, SR9009 was found to have REV-ERB-independent effects on cell proliferation and metabolism[25].

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