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Circadian Clocks Impact and Opportunities in Chronotherapeutic Drug Delivery Systems: A Short Review

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ABSTRACT

Circadian rhythm is a body's biological clock regulating body functions. It is a biological rhythm regulated by sunlight to drive the cyclic activities of the body like physiological, biochemical or behavioural processes. Chronopharmacology is an investigatory science that involves delivery of drugs based upon the circadian timing of biological events and rhythms. This biorhythm based medicine can maximize the therapeutic benefits and minimize adverse effects. Clinical disorders like stroke, cardiovascular diseases, bronchial asthma exacerbates its symptoms based on the biorhythm. So a timing based drug delivery is of utmost importance to treat circadian based diseases. Chronotherapeutics is a time dependent drug pharmacokinetics that is programmed, time controlled, pulsed to optimize better therapeutic effects. This review addresses circadian rhythm, molecular mechanisms controlling it, its influence on body functions, circadian exacerbation of symptoms and programmed drug delivery systems.

Key words: Circadian rhythm, Biorhythm based medicine, Drug delivery system, Chronopharmacokinetics

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INTRODUCTION

Circadian rhythm is a generic function of a living organism that oscillates around a 12-24 hr clock. Researchers have proved that all living organisms in this world have an inborn rhythm within themselves with varying frequencies that ranges from one season to another. This biorhythm is also a characteristic feature of the human body also. This rhythm determines sleep and wakefulness, feeding behavior and can alter lung functions, blood pressure, cardiac functions, body temperature, blood counts, neuronal activity, cell regeneration, hormone synthesis and other biological activities in the human body. These biological processes governed by the circadian rhythm including the sleep wake cycle are controlled by the suprachiasmatic nucleus (SCN) of hypothalamus. The molecular mechanism behind this biological rhythm is determined by the presence of clock genes namely Per 1, Per 2, Per 3 expressed in the SCN nucleus. The pathophysiology of many diseases like bronchial asthma, allergic rhinitis, cardiovascular diseases, arthritis, peptic ulceration etc. also exacerbates its symptoms based on the timing based on biological rhythm [1]. Bronchial asthma is one of the commonest disorders that increases airway resistance based on the timing of biological clocks. There is a 40 % increase in risk of myocardial infarction and 40% increased risk between 6 am and noon and cardiac death is more frequent in early morning hours.

Chronopharmacology

Chronopharmacology is an investigatory science that involves delivery of drugs based upon the timing of biological events and rhythms. Chronotherapeutics refers to invivo drug availability that is timed to match the biorhythm of disease and its symptoms [2]. This treatment is done to a patient according to the diurnal change in a person's daily, monthly, yearly and seasonal biological clock, so that the patient obtains maximum health benefits and minimizes the side effects [2,3].

Timed release of theophylline dose at 3 pm and inhaled corticosteroid during 5.30 pm is

an effective protocol in asthmatic treatment. Similarly administration of H2 antagonist drug at bed time reduces acid secretion and heals peptic ulcer. There can be reduction in BP with morning dose of Enapril and HMG-Co A reductase inhibitor is more effective with dose in the evening.

Administration of anti-inflammatory drugs (NSAIDs) like Indomethacin and ketoprofen, have shown to have greater rate and bioavailability when administered in the mornings than in evenings. This is because of controlled release of Indomethacin and Ketoprofen has been observed with better morning absorption [3-5].

Molecular mechanism governing circadian rhythm

A Nobel prize in Physiology was jointly awarded in 2017 for Jeffrey C.Hall, Michael Rosbash and Michael W. Young for their discoveries of molecular mechanisms that control circadian rhythm. The gene that regulates daily biological rhythm arises through an oscillating expression of a protein PERIOD, which accumulates at night in the cells and degrades throughout the day [3,6].

Animals, plants and also few prokaryotic organisms also regulate this circadian rhythm in physiological and metabolic activities and genetic expressions etc. The circadian clocks have three basic pathways, an input receiving environmental signal to an central circadian oscillator that maintains the timing of the circadian clock which in turn activates an output pathway that controls the physiological, behavioural, psychological and genetic processes inside the body [3,6]. The genetic and molecular mechanisms governing this gene were first identified and isolated as the first clock gene from Drosophila, period (Per) for its expression in circadian timing [7].

From afternoon, the two basic helical loop helix and PAS domain transcription factor, the CLOCK and CYCLE heterodimers bind with the regulatory elements (CACGTG), which then activates the per and tim transcription. The per and tim mRNA levels keep accumulating in the night. PER gene is phosphorylated by DOUBLE-TIME kinase is targeted for its degradation by ubiquitin/proteasome pathway [8].

The light-induced conformational change that occurs in the blue-light photoreceptor cryptochrome (CRY) promotes the formation of CRY-TIM complexes and TIM degradation by ubiquitin/proteasome pathway [8,9].

Suprachiasmatic nucleus governs the circadian clock. Melatonin, hormone that is released by the pineal gland, is one example of a multisynaptic output of the SCN [10].

Pharmaceutics is research area of biomedical with pharmaceutical sciences dealing with designing and evaluation of pharmaceutical drug dosage forms to guarantee a safer and effective, reliable health care. A chronopharmaceutical drug delivery systems symbolizes time-controlled and target specific drug delivery systems [11,12].

Ideal characteristics of circadian timing based drug delivery system [13]

✓ The drug must be nontoxic.

✓ It should have a self-regulated feedback controlled system.

✓ It should be biocompatible and biodegradable.

✓ It should be easy to manufacture at low financial cost.

✓ It should have a real time and specific activated biomarker for a given disease.

This chronotherapeutic medication aims at evenly spaced time intervals for a day cycle in an attempt to allow constant drug delivery throughout a 24 hour period, so that the medications would work maximally and effectively [13,14].

Chronopharmaceutical models

A number of chronopharmaceutical modeling approaches are now available in the regulation, cancer chemotherapy, and glucose concentration control and cardiovascular diseases which are subjected to various advantages and disadvantages. But the discovery chronotherapeutic models like controlled release formulations have been beneficial. These formulations come under 2 types, that can be divided into subgroups namely rate-controlled release, delayed-release and pulsed-release formulations [15–17].

A three layered semipermeable polymeric coating was developed to allow biphasic drug release. This kind of three layer formulation has been beneficial in the administration of L-- dopa in Parkinsonian patients [18].

Enteric coatings are based on time-controlled drug administration and are pH sensitive. This is beneficial in the treatment of nocturnal asthma where salbutamol in a barrier coating that works intestinal pH level at 6 is found to be therapeutically useful [18,19]. A sigmoidal release systems is a pellet type preparation where an active organic acid is with an insoluble polymer to achieve different time lag [20].

Another system of drug delivery was a Hydrogel system which is a three dimensional structures composed of hydrophilic polymers that can imbibe water as drug-delivery systems. Hydrogel-based delivery devices is beneficial for ocular, oral, epidermal, rectal and subcutaneous applications [13,20].

Chronopharmaceutical technologies

The Chronopharmaceutical technologies are CONTINR, CODAS, OROSR, CEFORMR, DIFFUCAPSR, TIMERxR, Physico-chemical modification of the API: etc. CONTIN technology has enabled tablet form of timing based sustained release of drugs like aminophylline, theophylline etc. OROSR technology is a tablet with two layers an active drug layer and a layer of osmotically active agents with a pre-programmed, controlled drug delivery into the gastrointestinal tract [21]. The CODASR technology works as an extended release capsule. Eg. Verapamil uses this strategy to reduce BP in the morning compared with other time intervals [21-26].

The Physico-chemical modification of API aims at modification of physicochemical properties like membrane permeability, solubility, partition coefficient to achieve the chronopharmaceutical objective [5]. An example of such technology is the use of HMG-CoA reductase inhibitors (antihyperlipidemic statins) and antiulcerative agents. CEFORMR technology utilizes a uniformly sized and shaped microspheres of pharmaceutical compounds coated for controlled release with enteric coating with combination of fast/slow release combination. This strategy has used in the development CardizemR LA, i.e., 1-day diltiazem formulation.

DIFFUCAPSR technology is a unit dosage capsule form for delivering drugs containing beads, pellets, granules, etc in a circadian timing based release fashion. This technology developed the formulation of propranolol that contains Chronotherapeutic drug delivery system for treatment of hypertension. Another technology called TIMERxR is a hydrophilic type of system that combines xanthan and locust bean gums mixed with dextrose. The drug release in this strategy is controlled by the rate of water penetration in the alimentary tract into the TIMERxR gum matrix that expands to form a gel and instantaneously causes release of the drug. This strategy has been used in the development of an oral, CR opioid analgesic oxymorphone and AD 121 in the treatment of rheumatoid arthritis [17].

CONCLUSION

Chronotherapeutics, a circadian based medicine is a newer form of medicine evolved to benefit with maximized use of drugs with improved patient care and reduce the drug dosage. The development of various strategies which are pulsed, time controlled and programmed delivery have wide applications in different diseased states. This chronotherapeutic drug delivery system is an ideal system that releases the drug at the right time at the specific targeted site with the right dose. Since this area seems to be utmost beneficial to patients, this remains as an important research area of continuous research.

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