CHRONOTHERAPY: AN APPROACH TO SYNCHRONIZE DRUG DELIVERY WITH CIRCADIAN RHYTHM

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Abstract

The existence of circadian rhythms in nature and their influence on biological systems in man have given rise to the concept of chronotherapy; the science of delivering drugs in synchrony with the rhythm-dependent circadian variation inherent in the human body. Circadian rhythms vary amongst organ systems which influences the time at which the most severe symptoms of chronic medical conditions are experienced. Some of these chronic diseases that have been studied are asthma, rheumatoid arthritis, cardiovascular disease peptic ulcer, hypercholesterolemia, allergic rhinitis, mood disorders, diabetes and cancer. Various technologies are adopted to mimic circadian rhythms of pathophysiological state of human biological system. This review is focused on basic physiology of circadian rhythms and technological development in the field of chronotherapeutic drug delivery systems (CDDS).

Key Words: Circadian rhythms; Time controlled release systems; Stimuli induced systems; External stimuli dependent system

Introduction

Matching drug release to the body’s circadian rhythms has been the elusive goal of a select band of drug delivery. The idea of targeting release to the specific time of day when there is maximal clinical manifestation of a disease has obvious advantages, and there is no shortage of ingenuity in designing formulations for time-delayed drug release. Mammalian circadian pacemakers influence a multitude of biological processes, including the sleep-wake rhythm. Clock genes are the genes that control the circadian rhythms in physiology and behavior.

The effectiveness and toxicity of many drugs vary depending on dosing time associated with 24 hr rhythms of biochemical, physiological and behavioral processes under the control of circadian clock. Such chronopharmacological phenomena are influenced by not only the pharmacokinetics but also pharmacodynamics of medications. Identification of a rhythmic marker for selecting dosing time will lead to improved progress and diffusion of chronopharmacotherapy. The mechanisms underlying chronopharmacological findings should be clarified from viewpoint of clock genes. On the other hand, several drugs have an effect on circadian clock. The knowledge of interactions between circadian clock and drug should be very useful for the clinical practice.

Biological Clock

All humans are synchronized to the rhythmic light-dark changes that occur on a daily basis. Rhythms in physiological and biochemical processes and behavioral patterns persist in the absence of all external 24-hour signals from the physical
environment, with a period that is close to 24 hours. These rhythms are referred to as ‘circadian, from the Latin ‘circa diem’ (about a day), and are attributable to internal biological clocks, driven by a major circadian pacemaker in the brain. The circadian pacemaker is entrained each day to the 24-hour solar cycle, which is the major ‘zeitgeber’ (literally time-giver). Other zeitgebers are food intake, activity, or social cues, e.g. the alarm clock. Good temporal entrainment allows for optimal performance at the right time of the day, because being able to anticipate future tasks allows the appropriate physiological and psychological preparation. However, our modern society often imposes deviations from the regular work-rest-scheme, as in shift work, which results in problems with entrainment. Table 1 shows the peak time of function of various physiological processes in the body.

Table 1. Human Circadian time structure

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Peak time of functions</th>
</tr>
</thead>
</table>
| Midnight | Thyroid stimulating hormone  
Growth hormone  
Melatonin, Prolactin  
Lymphocytes  
Atrial natriuretic peptide  
Eosinophils  
Adrenocortical tropic hormone  
Follicle stimulating hormone, Luteinizing hormone  
Cortisol, Testosterone  
Plasma renin activity  
Aldosterone, Angiotensin  
Catecholamines  
Blood pressure/Heart rate  
Arterial compliance/Nasal resistance  
Platelet adhesiveness  
Blood viscosity  
Haemoglobin, Serum iron  
Serum total proteins  
Airway patency (Peak expiratory flow, forced expiratory volume in 1 s)  
Insulin  
Respiratory rate  
Body temperature  
Triglycerides |
| 6 AM     | Cholesterol  
Diuresis  
Blood flow (forearm)  
Neutrophils  
Basal gastric acid secretion  
Calcitonin gene-related peptide  
White blood cells |
| Noon     | 6 PM |

Failure to adapt to environmental and societal time cues leads to misalignment of internal biological clocks. This ‘dysentrainment’ comes with enhanced risk of errors and accidents, loss of productivity, and health risks such as increased propensity for cancer, depression, sleep disturbances, gastrointestinal, metabolic and cardiovascular disorders, decreased immune responses and even life span. Hence, people with circadian rhythm disruption caused by shift work often develop glucose intolerance, diabetes and hypertension, and maybe cancer. The recent discovery of the core molecular circadian clock machinery has dramatically increased interest in the impact of circadian dysregulation on mental and physical health.

Molecular basis of circadian rhythms

Circadian rhythms are directed by a master biological clock in a specific brain structure of the hypothalamus called the suprachiasmatic nuclei (SCN). Apart from the SCN, the body has circadian oscillators in all brain regions and peripheral tissues, for example the liver. The SCN is synchronised daily by environmental signals – mainly light. Receiving information on lighting conditions directly from the retina, the SCN drives secretion of the pineal gland hormone melatonin as well as and many peripheral clocks, and their outputs modulate the SCN through feedback or feed-forward effects. Thus, in the body there is a hierarchy of interacting clocks.

In all cells, the expression of many genes changes rhythmically over 24 hours. Specific circadian genes such as CLOCK, BMAL1, and PER are responsible for the main SCN clock working machinery as well as subsidiary clocks in other parts of the body. In mice with mutations in time-keeping genes, deviant circadian sleep-wake and other rhythms can be observed. In addition, new interest in the role of circadian dysregulation in psychiatric disorders has arisen from the finding that a mutation in a core
circadian clock gene induces hyperactivity, decreased sleep, and mania-like behaviour in mice\(^5\).

Animal studies were the key development that brought the field to its present exciting position, because their findings suggested that ‘clock genes’ are directing the circadian rhythms in all physiological processes.

**Implication of Circadian rhythm in disease manifestation**

The idea of homeostasis is based in the history of early medical research when methods, technology and diagnostic tools had not yet reached the stage of development to adequately highlight the importance of inter- and intra-individual variability. Circadian rhythms are not homeostatic in nature and vary amongst organ systems. As a result, day-night patterns influence the occurrence and severity of many chronic diseases\(^6\), which may influence the manner in which they are managed. Many diseases are affected by the biological rhythm and show circadian symptoms intensity. Gout and peptic ulcer attacks are most common at night\(^7\). Acute pulmonary edema, congestive heart failure, and asthma worsen nocturnally\(^8,9\). Signs of allergic rhinitis and rheumatoid arthritis are stronger overnight or in the morning at the time of wakening\(^10-12\). Deadly pulmonary embolism, stroke and hypertensive crises are common to occur in the morning\(^13,14\). Depression is also seen more in the morning\(^15\). Osteoarthritis symptoms worsen during daily activities becoming intense distinctively in the late afternoon and in the evening\(^16\). Bleeding ulcers is more regular in the afternoon than in the morning\(^17\).

Table 2 comprises different therapeutic category along with examples of drug molecule which influence by circadian rhythm.

<table>
<thead>
<tr>
<th>Therapeutic Class</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti asthmatic agents</td>
<td>Theophylline, Terbutaline sulfahte</td>
</tr>
<tr>
<td>Cardiovascular drugs</td>
<td>Enalapril, diltiazem, nifedipine, propanolol, verapamil</td>
</tr>
<tr>
<td>Anticholesterolmic drugs</td>
<td>Lovastatin, Simvastatin</td>
</tr>
<tr>
<td>Gastro-intestinal agents</td>
<td>Ranitidine, omeprazole, Cemitidine, famotidine</td>
</tr>
<tr>
<td>Anti cancer agents</td>
<td>Doxorubicin, Cisplatin, methotrexate</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>Ibuprofen, indomethacin, tenoxicam, acetylsalicylic acid</td>
</tr>
</tbody>
</table>

**Chronotherapeutic drug delivery systems (CDDS)**

An ideal CDDS should provide specific release of active moiety according to circadian rhythms of the disease state. It should get easily metabolized or ejected out from the body after release of the drug. It should be non-toxic and biocompatible, easy to manufacture, easy to administer and economical. It should improve patient compliance.

CDDS can be classified into three major categories:

1. Time controlled release systems
2. Stimuli induced systems
   - Thermo-Responsive systems
   - Chemical stimuli induced systems
3. External stimuli dependent system
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i. Electro responsive systems

ii. Micro electro mechanical systems (MEMS)

iii. Magnetically induced systems

These systems are gaining popularity day by day. Different technology has been adopted by various companies to develop a perfect CDDS. Table 3 shows examples of such technologies with their rational of formulation.

Table 3. Marketed products of CDDS

<table>
<thead>
<tr>
<th>Technology</th>
<th>Rationale</th>
<th>Products</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONTIN®</td>
<td>Drug blended with hydrophilic cellulose, then hydrated with polar solvent and fixed with a higher aliphatic alcohol to produce a semi-permeable matrix with uniform porosity.</td>
<td>Uniphyl® once daily theophylline MS Contin® and Oxycontin® for use in pain management.</td>
<td>Purdue Frederick, Norfolk, CT, USA</td>
</tr>
<tr>
<td>CODAS®</td>
<td>Chronotherapeutical oral drug absorption system consisting of drug loaded beads that are coated with release-controlling polymer. Polymer consists of water-soluble and water-insoluble polymers to induce a lag time.</td>
<td>Verelan® PA containing verapamil for use in hypertension.</td>
<td>Elan Drug Technologies, San Francisco, CA, USA</td>
</tr>
<tr>
<td>CEFORM®</td>
<td>Biodegradable polymers/bioactives are subjected to varying temperature, thermal gradients and flow processes to produce microspheres of uniform size and shape (150-180μm)</td>
<td>Cardizem® LM containing diltiazem for use in hypertension.</td>
<td>Fuisz Technologies, Chantilly, VA, USA</td>
</tr>
<tr>
<td>DIFFUCAPS®</td>
<td>A multiparticulate system consisting of an inactive core, coated with an active pharmaceutical ingredient mixed with a water-soluble composition. This may be in the form of beads, pellets or granules.</td>
<td>Innopran® XL containing Propranolol for use in hypertension.</td>
<td>Eurand Pharmaceuticals LTD, Dayton, Ohio, USA</td>
</tr>
<tr>
<td>GEOMATRIX®</td>
<td>The controlled release is achieved by constructing a multilayered tablet made of two basic key components; 1) hydrophilic polymers such as hydroxypropyl methylcellulose (HPMC) and 2) surface controlling barrier layers. Active loaded core surface that is available for drug relase when exposed to the fluid is controlled by barrier layers.</td>
<td>Sular® (nisoldipine CR) &amp; Coruno® (molsidomine).</td>
<td>SkyePharma, Muttenz, Switzerland</td>
</tr>
<tr>
<td>TIMERx®</td>
<td>A novel polysaccharide system that adopts the use of xanthan gum and locust bean gum in the presence of secondary and tertiary components, to form water-soluble granules. ‘Tablet within a tablet’ to obtain different chronotherapeutic profiles. Geminex® is an improvement which provides the potential for dual therapy.</td>
<td></td>
<td>Penwest Pharmaceuticals, Danbury, CT, USA</td>
</tr>
</tbody>
</table>
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| **OROS**<sup>®</sup> | As osmotic pump system comprising a central drug reservoir surrounded by a semi-permeable membrane, which is surrounded by osmotically active agents in tablets with a strategically laser-drilled orifice. | Covera<sup>®</sup> HS containing verapamil for use in hypertension | Alza Corporation, Mountainview, CA, USA |
| **PULSINCAP**<sup>®</sup> | Consists of a drug reservoir housed within a water-soluble capsule body. The open end is plugged with swellable polymers that are pushed out when in contact with fluid, releasing drug from the reservoir. | A versatile system that can create lag times as well as allowing tablets/minitablets, solutions or beads to be housed within the capsule body. | R.P. Scherer International Corporation, Troy, MI, USA |
| **PULSYS**<sup>™</sup> | A novel pulsatile release technology that consists of one immediate-release and two delayed-release components with the use of soluble and insoluble coatings. | Moxatag<sup>™</sup> containing amoxicillin for use in antibiotic therapy. | Middlebrook Pharmaceuticals, Westlake, Texas, USA |

### Time controlled release systems

In time controlled drug delivery systems release is obtained after a specific time interval inorder to mimic the circadian rhythm. Both single and multiparticulate CDDS system has been developed. Such type of CDDS contains two components: one is of immediate release type and other one is a pulsed release type<sup>21,22</sup>.

**Stimuli induced systems**

Several polymeric delivery systems undergo phase transitions and demonstrate marked swelling-deswelling changes in response to environmental changes including solvent composition ionic strength, temperature, electric fields, and light<sup>23</sup>.

Responsive drug release from those systems results from the stimuli-induced changes in the gels or in the micelles, which may deswell, swell, or erode in response to the respective stimuli. The mechanism of drug release include ejection of the drug from the gel as the fluid phase synereses out, drug diffusion along a concentration gradient, electrophoresis of charged drugs towards an oppositely electrode and liberation of the entrapped drug as the gel or micelle complex erodes. These systems are further classified in to temperature induced systems and chemical stimuli induced system, on the basis of stimulus.

**Thermo-Responsive systems**

Temperature is the most widely used triggered signal for variety of stimuli induced systems. The use of temperature as a signal has been justified by the fact that the body temperature often deviates from the physiological temperature (37 °C) in the presence of pathogens or pyrogens. This deviation sometimes can be a useful stimulus that activates the release of therapeutic agents from various temperature-responsive drug delivery systems for disease accompanying fever. The drug delivery systems that are responsive to temperature utilize various polymer properties, including the thermally reversible coil/globule transition of polymer molecules, swelling change of networks, glass transition and crystalline melting<sup>24-27</sup>.

**Chemical stimuli induced systems**

Different systems have been developed to regulate drug release via chemical such as Glucose-responsive insulin release devices, Inflammation-induced release system, pH sensitive drug delivery system and Drug release from intelligent gels responding to antibody concentration.

In case of Diabetes mellitus, there is rhythmic increase in the levels of glucose in the body, requiring injection of the insulin at proper time. Several systems have been developed which are able to respond to changes in glucose concentration. One such system includes pH sensitive hydrogel containing glucose oxidase immobilized in the hydrogel. When glucose concentration in the blood increases glucose oxidase converts glucose into gluconic acid which changes the pH of the system.
This pH change induces swelling of the polymer which results in insulin release. On receiving any physical or chemical stress, such as injury, fracture etc., inflammation take place at the injured sites. During inflammation, hydroxyl radicals are produced from these inflammation-responsive cells. Degradation via hydroxyl radicals however, is usually dominant and rapid when Hyaluronic Acid gel is injected at inflammatory sites. Thus, it is possible to treat patients with inflammatory diseases like rheumatoid arthritis; using anti-inflammatory drug incorporated Hyaluronic Acid gels as new implantable drug delivery systems.

Recently, novel gels were developed which responded to the change in concentration of bioactive compounds to alter their swelling/deswelling characteristics. Special attention was given to antigen-antibody complex formation as the cross-linking units in the gel, since such interaction is very specific. Utilizing the difference in association constants between polymerized antibodies and naturally derived antibodies towards specific antigens, reversible gel swelling/deswelling and drug permeation changes occurs.

The pH sensitive drug delivery systems contain two components. The first is fast release type while the other is pulsed release which releases the drug in response to change in pH. In case of pH dependent system, advantage has been taken of the fact that there exists different pH environment at different parts of the gastrointestinal tract. By selecting the pH dependent polymers drug release at specific location can be obtained. Examples of pH dependent polymers include cellulose acetate phthalate, polyacrylates, and sodium carboxymethylcellulose. These polymers are used as enteric coating materials so as to provide release of drug in the small intestine.

External stimuli dependent systems

Electro-responsive systems

An electric field as an external stimulus has advantages such as the availability of equipment, which allows precise control with regards to the magnitude of current, duration of electric pulses. Electrically responsive system are prepared from polyelectrolytes (polymers which contain relatively high concentration of ionisable groups along the backbone chain) and are thus, pH-responsive as well as electro-responsive. Under the influence of electric field, electro-responsive hydrogels generally deswell or bend, depending on the shape of the gel lies parallel to the electrodes whereas deswelling occurs when the hydrogel lies perpendicular to the electrodes. Synthetic (partially hydrolyzed polyacrylamide, polydimethylaminopropyl acrylamide) as well as naturally (hyaluronic acid, chondroitin sulphate, agarose and carbomer) occurring polymers, separately or in combination, have been used.

Micro electro mechanical systems (MEMS)

MEMS biological applications are classified as either microfluidic devices or nonmicrofluidic devices. The ultimate goal of MEMS is to develop a microfabricated device with the ability to store and release multiple chemical substances on demand by a mechanism devoid of moving its parts. A wide variety of microreservoirs, micropumps, centilevers, rotors, channels, valves, sensors and other structures have been fabricated, typically from the material that have been demonstrated to be biocompatible and can be steriley fabricated and hermetically sealed.

Magnetically release induced systems

The use of an oscillating magnetic field to modulate the rates of drug release from polymer matrix was one of the old methodologies. Magnetic carriers receive their magnetic response to a magnetic field from incorporated materials such as magnetite, iron, nickel, cobalt etc. For biomedical applications, magnetic carriers must be water-based, biocompatible, non-toxic and non-immunogenic.

Conclusion

Conventional dosage forms do not treat diseases with chronological pathophysiology effectively. On the other hand, CDDS can easily mimic circadian rhythm of several diseases. Various approaches are employed to develop effective CDDS such as time controlled release systems, stimuli induced systems and external stimuli dependent systems. Chronotherapeutic delivery systems appear to have bright future as many pharmaceutical companies are developing such systems and already a number of chronotherapeutic products are available in the market.

Declaration of Interest

It is hereby declared that this paper does not have any conflict of interest.
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