Chronopharmacology and Chronopharmaceutical of Cardiovascular Diseases

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ABSTRACT

Cardiovascular functions such as heart rate and blood pressure show 24 h variation. The incidence of cardiovascular diseases including acute myocardial infarction and arrhythmia also exhibits diurnal variation. The centre of this circadian clock is located in the suprachiasmatic nucleus in the hypothalamus. However, recent findings revealed that each organ, including cardiovascular tissues, has its own internal clock, which has been termed a peripheral clock. The functional roles played by peripheral clocks have been reported recently. Since the peripheral clock is considered to play considerable roles in the processes of cardiac tissues, the identification of genes specifically regulated by this clock will provide insights into its role in the pathogenesis of cardiovascular disorders. In addition, the discovery of small compounds that modulate the peripheral clock will help to establish chronotherapeutic approaches. Understanding the biological relevance of the peripheral clock will provide novel approaches to the prevention and treatment of cardiovascular diseases. Such novel and more biological approaches to drug delivery may lead to safer and more efficient disease therapy in the future.

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INTRODUCTION

Cardiovascular functions such as heart rate (HR) and blood pressure (BP) show 24 h variation. The incidence of cardiovascular diseases such as acute myocardial infarction, strokes and arrhythmia also exhibits clear diurnal oscillation (Table no.1). Since most of these disorders can induce fatal or severe outcomes, it is important to elucidate the precise mechanism of the onset of these diseases. This circadian occurrence is believed to be tightly associated with an internal clock.

Table no.1 Common onset time of cardiovascular diseases

Diseases	Common onset time
Atrial fibrillation	Morning/night
Ventricular tachycardia/fibrillation	Morning
Acute coronary syndrome	Early morning
Pulmonary embolism	Early morning
Cerebral infarction	Morning
Subarachinoidal haemorrhage	Daytime

CIRCADIAN RHYTHM IN THE PATHOGENESIS OF CARDIOVASCULAR DISEASES

Studies using cardiomyopathic hamsters revealed that repeated phase shifts in the Light/Dark (L/D) cycle and disruption of rhythmicity strongly affected and shortened longevity [1, 2]. Martino et al. Used a murine model of pressure-overload cardiac hypertrophy (transverse aortic constriction (TAC)) [3]. They kept the mice in a rhythm disruptive 20-hour (LD 10:10) or normal 24-hour (LD 12:12) environment after TAC surgery. Rhythm-disturbed TAC mice exhibited a complete disruption of locomoter activity and could not consolidate the rhythm. Echocardiography reveals increased left ventricular end-systolic and diastolic dimensions with reduced contractility in rhythm-disturbed TAC animals. In addition, both perivascular and interstitial fibrosis were increased in rhythm disrupted mice. Interestingly, phenotypic rescue occurred when the external rhythm was normalized to 24-hour.

Blood pressure/hypertension

Blood pressure (BP) is well known to exhibit 24 h variation with a peak in the morning. A number of factors influence diurnal variation of BP. They include internal factors such as the autonomic nervous system [4], vasoactive intestinal peptide (VIP) [5], plasma cortisol [6], plasma renin activity [7], aldosterone [8] and plasma atrial natriuretic peptide (ANP) [9]. Both sympathetic activity and the renin–angiotensin–aldosterone axes peak in the early morning hours [4, 10]. In addition, BP is affected by a variety of external factors including physical activity, emotional state, meal and sleep/wake routine. These extrinsic stimuli also affect the autonomic nervous system, thus the 24-hour variation in BP is representative of both endogenous diurnal rhythm and exogenous factors.

Previously, Janssen et al. examined the role of the circadian clock in the BP rhythm, and demonstrated that a lesion of the rat SCN abolishes the circadian rhythm of BP and heart rate (HR) without affecting the 24-hour cycle of locomoter activities [11]. Recently, more detailed studies using mouse genetic technology provided insight into the role of clock system in BP regulation.

Woon et al. performed a genetic association study and demonstrated that single nucleotide polymorphisms within the BMAL1 promoter are associated with hypertension and type-2 diabetes [12]. Global deletion of BMAL1 completely abolished the rhythm of BP, and, in addition, this deletion resulted in a hypotensive phenotype due to reduced production of catecholamines [13]. However, endothelial specific deletion of BMAL1 did not alter the temporal oscillation of BP.

Wang et al. revealed a clear circadian expression of PPARγ in the aorta. They also identified that PPARγ binds to the BMAL1 promoter and transactivates.

Acute myocardial infarction/pulmonary embolism

It is well known that AMI or PE frequently occurs in the early morning [14, 15]. Thus, elucidating of the mechanisms of circadian variation of these disorders will lead to not only a better understanding of the pathogenesis of AMI or PE, but also to the development of preventive strategies [16]. A number of physiological functions exhibit diurnal variation, including BP, HR, coronary blood flow, platelet function, blood coagulability and fibrinolytic activity [16]. In the early morning, systemic BP and HR increase [17] and augment the oxygen demand of the heart. In addition, the vascular tone of the coronary artery rises and coronary blood flow decreases in the morning [18]. These increases in oxygen demand and decreases in oxygen supply exaggerate a mismatch of oxygen demand and supply in the morning. In addition, platelet function and blood coagulability also increase in the morning together with a reduction in fibrinolytic activity, resulting in a hypercoagulable state that could elicit the morning onset of thromboembolic events (Figure no.1). Accumulating evidence suggests that the autonomic nervous system plays a major role in the circadian variation of the onset of AMI. A morning increase in the frequency of ischemic episodes is absent in diabetic patients with autonomic nervous dysfunction [19]. Patients receiving β-blockers do not show morning increases in the incidence of angina, AMI and sudden death [20]. HR variability, which reflects sympathetic/vagal balance, is also associated with the onset of ischemic episodes in chronic stable angina [21]. Platelets are also involved in the variation of AMI or thromboembolic events [22]. Both circulating platelet numbers and their aggregation activity possess circadian oscillation. Platelet activation in vivo is induced by catecholamines secreted from the sympathetic nervous system in a circadian fashion. However, studies regarding platelet activation do not show a clear circadian expression of any surface markers characteristic of platelet activation. Therefore, it is unclear whether the internal clock system directly affects the circadian function of platelets.
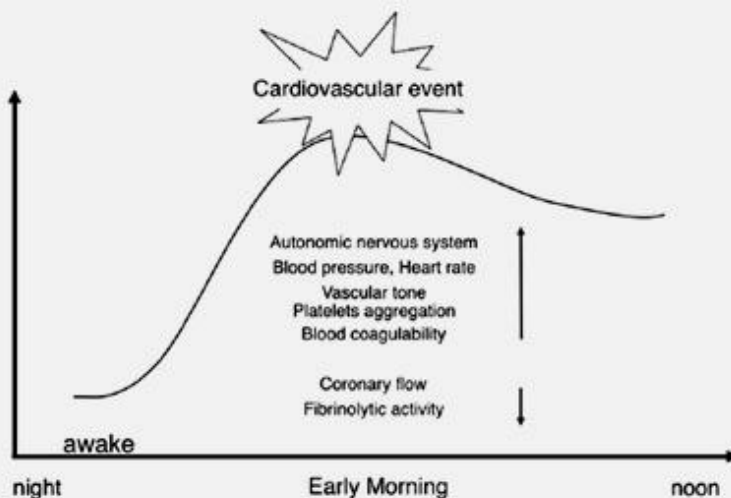
Figure no.1 In the early morning blood pressure and heart rate increase, then augment the oxygen demand of the heart. The vascular tone and blood coagulability also increase in the morning. these increases in oxygen demand and decreases in oxygen supply exaggerate a mismatch of oxygen demand and supply in the morning.

Arrhythmia [23]

A number of reports demonstrated the presence of circadian variation of cardiac arrhythmia. Portaluppi et al. extensively summarized about this topic. Accumulating evidence suggests that basic electrophysiological parameters have circadian variation. Atrial and ventricular refractory periods are strongly affected by the autonomic nervous system, in that sympathetic activity shortens it and parasympathetic activity elongates the period. Therefore, fluctuations in autonomic nervous system activity within a day can be a major trigger of circadian onset of cardiac arrhythmia. Each parameter of ECG was analyzed as to whether it has a diurnal variation. ECG or holter ECG, AV nodal function, QT interval, R and T wave voltage and QT interval have been shown to exhibit circadian variation. As for the onset of cardiac arrhythmia, paroxysmal atrial fibrillation (pAf) is categorized into two types: vagotonic pAf, which usually occurs at night, and adrenergic pAf, which occurs during the daytime. There are several reports showing different results in terms of peak period paroxysmal supra ventricular tachycardia (PSVT), from morning to midnight. However, they are consistent in that it is rare for PSVT to occur during the night time. Continuous holter monitoring of ECG revealed a 24-hour variation in the occurrence of ventricular premature beats (VPBs) with a peak between 6 a.m. and noon. Interestingly, the presence of a circadian onset of VPBs depends on left ventricular function. Only patients with a left ventricular ejection fraction greater than 30% have a circadian variation of VPBs. Goldstein et al. identified a clustering of VPBs between 6 and 10 a.m., however, they did not find any relationship between the onset of VPBs and cardiac mortality.

EXAMPLES OF CHRONOPHARMACEUTICAL TECHNOLOGIES

Currently key technologies in chronopharmaceutics includes: CONTINR, physico-chemical modification of the active pharmaceutical ingredient (API), OROSR, CODASR,

CEFORMR, DIFFUCAPSR, chronomodulating infusion pumps, TIMERxR, threedimensional printing, controlled-release (CR) erodible polymer and CR microchip strategies. Readers may find advantages and disadvantages of each technology depending on their specific needs on the website of each developer/marketer website before selection. Informations on FDA approval status and dosage formed were compiled from the FDA electronic orange book [24]. We will focus on the principle and application of each of these technologies.

CONTIN® technology

In this technology, molecular coordination complexes are formed between a cellulose polymer and a non-polar solid aliphatic alcohol optionally substituted with an aliphatic group by solvating the polymer with a volatile polar solvent and reacting the solvated cellulose polymer directly with the aliphatic alcohol, preferably as a melt. This constitutes the complex having utility as a matrix in controlled release formulations since it has a uniform porosity (semipermeable matrixes) which may be varied [25]. This technology has concretely enabled the development of tablet forms of sustained-release aminophylline, theophylline, morphine, and other drugs. CONTIN® technology provides for closer control over the amount of drug released to the bloodstream, and benefits patients in terms of reducing the number of doses they need to take every day, providing more effective control of their disease (particularly at night), and reducing unwanted side effects.

Physico-chemical modification of the API

In this strategy, a proprietary method is used to modify the physicochemical properties (e.g. solubility, partition coefficient, membrane permeability, etc.) of the API to achieve the chronopharmaceutical objective. The rationale for such approach is based on the published work demonstrating that solubility and permeability are critical factors governing drug bioavailability [26]. Typical examples of the use of this strategy in chronotherapy are those of antihyperlipidemic statins (HMG-CoA reductase inhibitors) and antiulcerative agents (histamine H2 receptor-antagonists).

OROS® technology

OROS® technology [27] uses an osmotic mechanism to provide pre-programmed, controlled drug delivery to the gastrointestinal tract. The dosage form comprises a wall that defines a compartment. The active drug is housed in a reservoir, surrounded by a semi-permeable membrane/wall (e.g. cellulose esters, cellulose ethers and cellulose ester–ethers) and formulated into a tablet. The tablet is divided into two layers, an active drug layer and a layer of osmotically active agents (e.g. poly(ethylene oxide)) comprising means for changing from a non-dispensable viscosity to a dispensable viscosity when contacted by fluid that enters the dosage form. For example, water from the gastrointestinal tract diffuses through the membrane at a controlled rate into the tablet core, causing the drug to be released in solution or suspension at a predetermined rate. This creates a 'pump' effect that pushes the active drug through a hole in the tablet. This technology, especially the OROS® Delayed Push– Pullk System,

also known as controlled onset extended release (COER) was used to design Covera- HSR, a novel anti-hypertensive product.

CODAS® technology

The Chronotherapeutic Oral Drug Absorption System (CODAS®) [28] is a multi-particular system which is designed for bedtime drug dosing, incorporating a 4–5 h delay in drug delivery. This delay is introduced by the level of non-enteric release-controlling polymer applied to drug loaded beads. The release controlling polymer is a combination of water soluble and water insoluble polymers. As water from the gastrointestinal tract comes into contact with the polymer coated beads, the water soluble polymer slowly dissolves and the drug diffuses through the resulting pores in the coating.

CEFORM® technology

The CEFORM® technology [29] allows the production of uniformly sized and shaped microspheres of pharmaceutical compounds. This ChrDDS approach is based on ''melt-spinning'', which means subjecting solid feedstock i.e. biodegradable polymer/bioactive agents combinations to the combination of temperature, thermal gradients, mechanical forces, flow, and flow rates during processing. The microspheres obtained are almost perfectly spherical, having a diameter that is typically 150–180 Am, and allow for high drug content. The microspheres can be used in a wide variety of dosage forms, including tablets, capsules, suspensions, effervescent tablets, and sachets. The microspheres may be coated for controlled release either with an enteric coating or combined into a fast/ slow release combination.

DIFFUCAPS® technology

In the DIFFUCAPS® technology [30], a unit dosage form, such as a capsule for delivering drugs into the body in a circadian release fashion, is comprising of one or more populations of drug-containing particles (beads, pellets, granules, etc. . .). Each bead population exhibits a pre-designed rapid or sustained release profile with or without a predetermined lag time of 3–5 h. The active core of the dosage form may comprise an inert particle or an acidic or alkaline buffer crystal (e.g. cellulose ethers), which is coated with an API-containing film-forming formulation and preferably a water-soluble film forming composition (e.g. hydroxyl propyl methyl cellulose, poly vinyl pyrrolidone) to form a water-soluble/dispersible particle. The active core may be prepared by granulating and milling and/or by extrusion and spheronization of a polymer composition containing the API.

Chronomodulating infusion pumps

Externally and internally controlled systems across a range of technologies including pre-programmed systems, as well as systems that are sensitive to modulated enzymatic or hydrolytic degradation, pH, magnetic fields, ultrasound, electric fields, temperature, light and mechanical stimulation have been reviewed in detail elsewhere [31]. To our knowledge infusion

pumps on the market that have been referred to as chronomodulating for drug delivery application include the MelodieR, programmable SynchromedR, PanomatR V5 infusion, and the RhythmicR pumps. The portable pumps are usually characterized by a light weigh (300–500 g) for easy portability and precision in drug delivery.

TIMERx® technology

The TIMERx® technology (hydrophilic system)[32] combines primarily xanthan and locust bean gums mixed with dextrose. The physical interaction between these components works to form a strong, binding gel in the presence of water. Drug release is controlled by the rate of water penetration from the gastrointestinal tract into the TIMERx® gum matrix, which expands to form a gel and subsequently releases the active drug substance. This system can precisely control the release of the active drug substance in a tablet by varying the proportion of the gums, together with the third component, the tablet coating and the tablet manufacturing process.

Three-dimensional printing®

Three dimensional printing® (3DP) is a novel technique used in the fabrication of complex oral dosage delivery pharmaceuticals based on solid freeform fabrication methods. It is possible to engineer devices with complicated internal geometries, varying densities, diffusivities, and chemicals [33]. Different types of complex oral drug delivery devices have been fabricated using the 3DP process: immediate-extended release tablets, pulse release, breakaway tablets, and dual pulsatory tablets. The enteric dual pulsatory tablets were constructed of one continuous enteric excipient phase into which diclofenac sodium was printed into two separated areas. These samples showed two pulses of release during in vitro with a lag time between pulses of about 4 h. This technology is the basis of the TheriForm® technology. The latter is a micro fabrication process that works a manner very similar to an ''ink-jet'' printer. It is a fully integrated computer-aided development and manufacturing process.

Other CR erodible polymers

Erodible polymers have been designed in different forms (e.g. tablets, capsules, microparticles) for ChrDDS applications. For example, Ross et al. [34] reported the development of a chronopharmaceutical capsule drug delivery system. The drug formulation is sealed inside the insoluble capsule body by an erodible tablet (ET) that is composed of an insoluble (e.g. dibasic calcium phosphate) and gel-forming (e.g. hydroxyl propyl methyl cellulos) excipient.

Controlled-release microchip

An alternative method to achieve pulsatile or chronopharmaceutical drug release involves using microfabrication technology. Santini et al. [34] reported a solid-state silicon microchip that can provide controlled release of single or multiple chemical substances on

demand. The release mechanism was based on the electrochemical dissolution of thin anode membranes covering microreservoirs filled with chemicals in solid, liquid or gel form. This technology has the potential to be used in the design of ChrDDS with a better control over drug release kinetic in order to match biological requirement over a versatile period of time.

CONCLUSION

Diurnal variations exist in the cardiovascular system at multiple levels including gene expression, protein expression and cellular and organ function. Since the internal clock seems to play a role in these cardiac tissues together with exogeneous factors, identification of genes specifically regulated by the circadian clock will provide insights into the role of this molecular mechanism in the cardiovascular system. In addition, the discovery of small compounds that are able to modulate the peripheral clock will help to establish chronotherapeutic approaches. Understanding the biological relevance of the internal clock will provide new insight into the development, prevention and treatment of cardiovascular disorders.

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