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The importance of circadian rhythms on drug response in hypertension and coronary heart disease—from mice and man

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Abstract

The cardiovascular system is highly organised in time; blood pressure (BP), heart rate (HR), peripheral resistance, pressure and the release/activity of vasodilating hormones all display pronounced circadian variations. Pathophysiological events within the cardiovascular system are also not random, as shown for instance by sudden cardiac death (SCD), stroke, ventricular arrhythmias (VA), arterial embolism, and symptoms of coronary heart disease (CHD) such as myocardial infarction (MI) and ischemia, angina attacks (AA) in stable angina (stA) or variant angina (varA) or silent ischemia. In hypertensive patients various anti-hypertensive drugs were investigated in crossover studies (morning vs. evening dosing); however consistent data were only obtained for angiotensin-converting enzyme (ACE) inhibitors and calcium channel blockers. Whereas in dippers ACE inhibitors had a super-dipping effect when dosed at night, no consistent difference in BP lowering effect on the 24-hr BP profile was found with calcium channel blockers after morning and evening dosing. In non-dippers the calcium channel blockers isradipine and amlodipine consistently transformed non-dippers into dippers, after evening dosing. Diuretics are also able to normalize a non-dipping behaviour. Moreover, a circadian phase-dependency in pharmacokinetics has been demonstrated for various cardiovascular active drugs such as β-blockers, calcium channel blockers, oral nitrates and ACE inhibitors, modified by the pharmaceutical formulation. There is evidence that in hypertensive dippers anti-hypertensive drugs should be given in the early morning, whereas in non-dippers it may be necessary to add an evening dose or even to use a single evening dose in order to not only reduce high BP but also to normalize a disturbed non-dipping 24 hr BP profile. In CHD, calcium channel blockers–mainly short acting and non-retarded preparations–seem to be less effective than β-adrenoceptor antagonists in reducing ischemic events during the night and early morning. However, the role of formulation and/or subclasses of the calcium channel blockers remains to be elucidated. In order to get more insight into the circadian regulation of the cardiovascular system animal models of primary and secondary hypertension have been studied in various strains of normotensive and hypertensive rats and mice. At least in rodents there is ample evidence that the 24-hr rhythms in BP and HR are under the control of biological clock(s) as they persist under constant darkness (i.e. in free-run conditions) with a period deviating from 24 hr; these rhythms are abolished by lesioning of the "master clock" located in the suprachiasmatic nulcei (SCN). In conclusion, chronobiological and chronopharmacological studies are important experimental and clinical approaches to get a better insight into the physiological and pathophysiologal regulation of the cardiovascular system including their rhythmic organisation. Circadian time-dependent clinical studies also have implications for drug therapy in hypertension and CHD.

Keywords: Blood pressure and heart rate rhythms; Human; Normotensive and hypertensive rats; Mice; Chronopharmacology; Biological rhythms

Abbreviations: AA, angina attacks; ABPM, ambulatory blood pressure measurement; AUC, area under the curve; BP, blood pressure; CHD, coronary heart disease; Cmax, peak drug concentration; DD, total darkness; GITS, gastro-intestinal therapeutic system; HR, heart rate; LD, light/dark schedule; MI, myocardial infarction; NE, norepinephrine; NO, nitric oxide; RAS, renin–angiotensin system; SCD, sudden cardiac death; SCN, suprachiasmatic nucleus; stA, stable angina; tmax, time-to-peak drug concentration; VA, ventricular arrhythmias; varA, variant angina; VPC, ventricular premature complex.

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Contents

1. Introduction

Living organisms are continuously influenced by external stimuli, many of which have rhythmic patterns. Environmental rhythms in daily and seasonal patterns of light, food availability and temperature, etc., are predictable and animals–including humans–have the ability to anticipate these environmental events with periodically and predictably changing internal conditions. These rhythmic patterns of anticipation have clear advantages and survival value (Strubbe & Woods, 2004). Thus, rhythmicity is the most ubiquitous feature of nature. Rhythms are found from unicellular to complex multicellular organisms both in plants, animals and men. The frequencies of rhythms in nature cover nearly every division of time. There are rhythms which oscillate once per second (e.g. in the electroencephalogram), once per several seconds (respiratory rhythm, heart rate [HR]), up to rhythms which oscillate once per year (circannual rhythm).

The most evident environmental change which results from the regular spin of the earth around its central axis and resulting in the alternation between day and night seems to have induced the predominant oscillation, the circadian rhythm (the about-24-hr rhythm; circa = about, dies = day, as proposed by Halberg, 1959, 1969). There is sound evidence that living systems including humans are not only organized in space but are also highly organized in time.

Circadian rhythms have been documented throughout the plant and animal kingdom at every level of eukariotic organization. Circadian rhythms by definition are endogenous in nature, driven by oscillators or clocks (Aschoff, 1954. 1963a, 1963b, 1965), and persist under free-running conditions. In various species (*Drosophila melanogaster*, Neurospora, mouse, golden hamster) the genes controlling circadian rhythms have been identified (genes: *per*, *frq*, *clock*, *tau*). In 1971 Konopka and Benzer (Konopka & Benzer, 1971) were able to identify on the X chromosome of *Drosophila*, a region which controlled the period in the eclosion rhythm of 3 mutants (per clock gene). In 1984 Bargiello et al. demonstrated that a fragment of the per gene injected into embryos of an arrhythmic mutant of *Drosophila* could restore rhythmicity in eclosion (Bargiello et al., 1984). This data provided the first evidence that the biological clock is genetically determined and can even be transplanted from 1 animal to another, thereby inducing the rhythmicity of the donor to the recipient.

Circadian clocks are believed to have evolved in parallel with the geological history of the earth, and have undergone selection pressures imposed by cyclic factors in the environment. These clocks regulate a wide variety of behavioral and metabolic processes in many life forms (Edmunds, 1997; Hastings, 1997). They enhance the fitness of organisms by improving their ability to efficiently anticipate periodic events in their external environments, especially periodic changes in light, temperature and humidity.

The mammalian circadian clock, located in the neurons of suprachiasmatic nuclei (SCN) in the brain and in cells of peripheral tissues is driven by a self-sustained molecular oscillator, which generates rhythmic gene expression with a periodicity of about 24 hr (Reppert & Weaver, 2002; Hastings & Herzog, 2004). This molecular oscillator is composed of interacting positive and negative transcription/translation feedback loops (Rensing, 1997; Hastings, 2003; Hardin, 2004) in which the heterodimeric transcription activator CLOCK/BMAL1 promotes the transcription of E-box containing Cryptochrome (Cry1 and Cry2) and Period (Per1 and Per2)