Pharmacogenomics and circadian rhythms as mediators of cardiovascular drug-drug interactions

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ABSTRACT

This article summarizes the current literature and documents new evidence concerning drug-drug interactions (DDI) stemming from pharmacogenomic and circadian rhythm determinants of therapies used to treat common cardiovascular diseases (CVD), such as atherosclerosis and hypertension. Patients with CVD often have more than one pathophysiologic condition, namely metabolic syndromes, hypertension, hyperlipidemia, and hyperglycemia, among others, which necessitate polytherapeutic or polypharmaceutic management. Interactions between drugs, drugs and food/food supplements, or drugs and genetic/epigenetic factors may have adverse impacts on the cardiovascular and other systems of the body. The mechanisms underlying cardiovascular DDI may involve the formation of a complex pharmacointeractome, including the absorption, distribution, metabolism, and elimination of drugs, which affect their respective bioavailability, efficacy, and/or harmful metabolites. The pharmacointeractome of cardiovascular drugs is likely operated with endogenous rhythms controlled by circadian clock genes. Basic and clinical investigations have improved the knowledge and understanding of cardiovascular pharmacogenomics and pharmacointeractomes, and additionally they have presented new evidence that the staging of deterministic circadian rhythms, according to the dosing time of drugs, e.g., upon awakening vs. at bedtime, cannot only differentially impact their pharmacokinetics and pharmacodynamics but also mediate agonistic/synergetic or antagonistic DDI. To properly manage CVD patients and avoid DDI, it is important that clinicians have sufficient knowledge of their multiple risk factors, i.e., age, gender, and life style elements (like diet, smoking, psychological stress, and alcohol consumption), and comorbidities, such as diabetes, hypertension, dyslipidemia, and depression, and the potential interactions between genetic or epigenetic background of their prescribed therapeutics.

1. Introduction

According to The World Health Organization, cardiovascular diseases (CVD) are the leading cause of mortality worldwide (https://www.who.int/health-topics/cardiovascular-diseases). Atherosclerosis and hypertension are the two most common chronic vascular diseases that contribute to the occurrence of myocardial and cerebral infarctions, the two primary life-threatening emergencies. Significant progress has been made in the prevention and treatment of CVD through decades of efforts in basic science and technological innovation as well as public health education. Successful strategies implemented for mitigating CVD include life-style changes, identification and control of risk factors, and more

effective medications and other interventions. Although the incidence of CVD, compared to other medical conditions, in the United States and other developed countries has shown a decline during the past few decades, it continues to be the primary disease with highest morbidity and mortality according to The Center of Disease Control (CDC) report 2020 (https://www.cdc.gov/heartdisease/facts.htm). Moreover, in other countries with emerging economies, the prevalence and mortality of CVD are rising in alarming rates.

Patients with CVD often have more than one pathophysiologic condition, such as metabolic syndromes characterized by obesity, hypertension, hyperlipidemia, and hyperglycemia. Pathogenic insults promote phenotypic contractile, synthetic, proliferative, and apoptotic changes of

the arterial and heart tissues (Geng, 1997, 2001, 2003; Geng and Libby, 2002). Drug-drug, drug-food/food supplement, or drug-genetic/epigenetic factor interactions may result in adverse impacts on the cardiovascular system (Turner et al., 2020). In 1995, Leape et al. (1995) conducted a systematic analysis of adverse drug events (ADEs), estimating that drug-drug interactions (DDI) account for 3–5% of all in-hospital medication errors. Raschetti et al. (1999) additionally reported that adverse DDI are an important cause of patient visits to emergency medical departments or hospital admissions. In 2016, the American Heart Association (AHA) issued a scientific statement (Wiggins et al., 2016; Benes et al., 2016) concerning the cardiovascular DDI of cholesterol-lowering statins and its importance in patient care. Here, we summarize the current literature and document new evidence for cardiovascular DDI stemming from underlying pharmacogenomic and circadian rhythm determinants.

2. Polypharmacology, pharmacogenomics, and pharmacointeractomes

2.1. Common cardiovascular drug interactions

Cardiovascular DDI occur when multiple therapeutics administered concomitantly act synergistically or in opposition to impact efficacy or safety. The mechanisms of DDI involve drug absorption, distribution, metabolism, and elimination that affect bioavailability and efficacy, and/or production of unwanted/harmful metabolites (Fig. 1). DDI that decrease the effect of one or more medications used in combination are termed antagonistic and those that enhance the effect of one or more medications used in combination are termed synergistic or agonistic. Several medications prescribed for the prevention and treatment of diseases of the cardiovascular system are highly interactive (Table 1). Moreover, multi-morbidity is linked with the high prevalence of polypharmacy (Turner et al., 2020). Accordingly, it is not unusual for older patients with atherosclerosis-associated ischemic heart failure to receive a sizeable combination of cardiovascular therapeutics, e.g., heart failure drugs like digoxin, a cholesterol-lowering drug like simvastatin, one or more blood pressure (BP)-lowering drugs like an angiotensin-converting enzyme inhibitor (ACEI), angiotensin II receptor blocker (ARB), beta blocker, and/or diuretic, and an antiplatelet like aspirin and an anti-coagulant such as warfarin or clopidogrel (Turner et al., 2020).

2.2. Pharmacogenomics of cardiovascular diseases and drug therapies

Genetic codes reside in the DNA sequence. Recent advances in next-

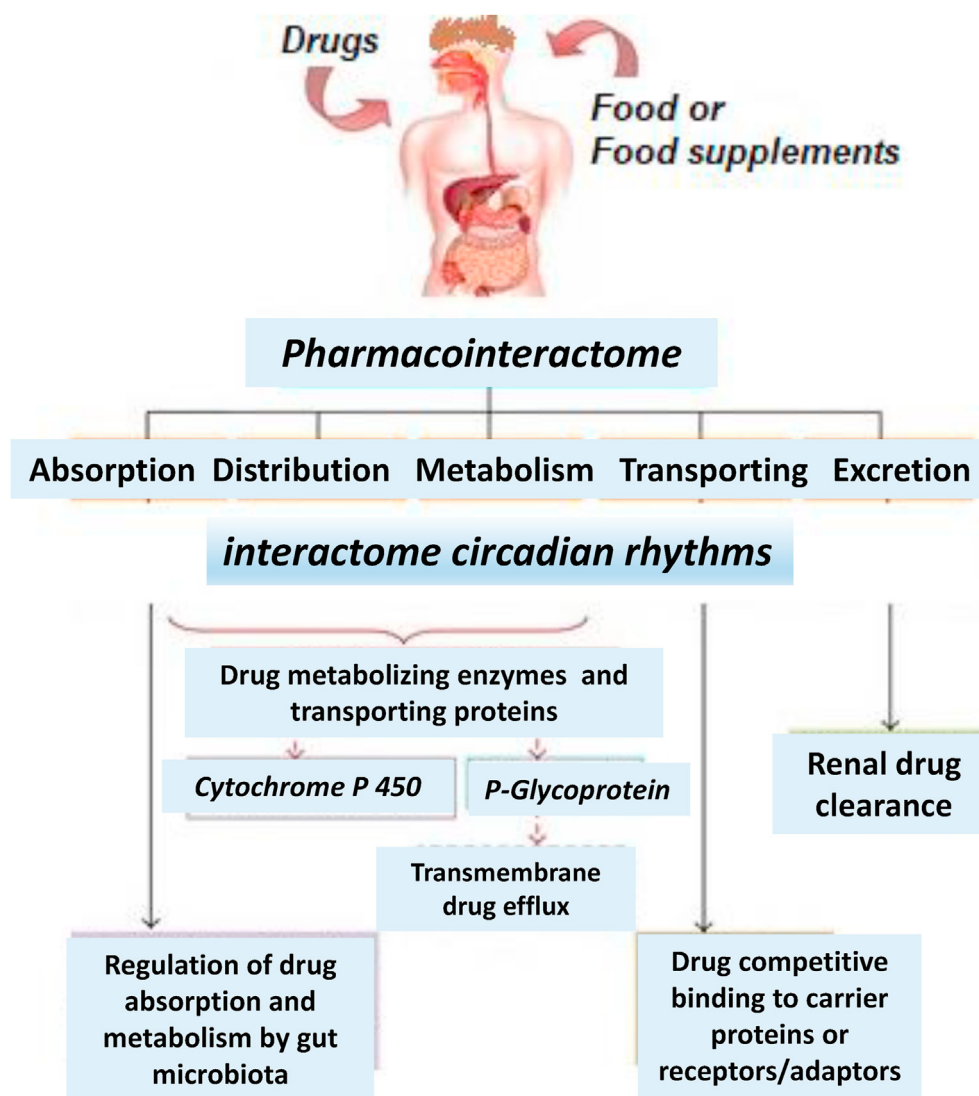**Fig. 1.** Schematic representation of pharmacological interactomes (pharmacointeractone) for cardiovascular drug interaction. Genomic and other omics profiling data reveal pharmacological "interactome" networks that define the drug molecular interactions; drug distribution, metabolism, transportation, excretion; and disease associations with possible therapeutic targets, which often operate with circadian rhythms.

Table 1
Agonistic and antagonistic-like DDI of therapies commonly prescribed to treat cardiovascular disease[a].

Drug/ Classes	Agonistic-Like Interaction	Antagonistic-Like Interaction
Digoxin	Diuretics, Antiarrhythmics, Macrolide antibiotics, Cholestyramine, Neomycin, Keto- and intraconazole, Calcium antagonists, Cyclosporine, Indomethacin, HMG CoA reductase inhibitors, Benzodiazepines, Amiodarone, Verapamil	Rifampicin, Antacids (liquid)
Warfarin	Furosemide, Amiodarone, Sulfa, Macrolide and quinolone antibiotics, NSAIDs	Azathioprine, Phenobarbitone, Carbamazepine, Dexamethasone, Prednisolone, Rifampicin, Vitamin K, Raloxifene
Clopidogrel	Rifampicin, Caffeine, Methylxanthines, Phosphodiesterase inhibitors	Statins, Calcium channel blockers, Warfarin, Proton pump inhibitors
ACEI	NSAIDs, Probenecid, Calcium channel blockers	Indomethacin, Antacids (liquid),
β-blockers	Amiodarone, Calcium channel blockers, Diltiazem, Phenoxybenzamine	Phenobarbital, Rifampicin, Cimetidine, Antacids (liquid), NSAIDs
Statins	Amiodarone, Verapamil, Fibrates, Amprenavir, Diltiazem	Nevirapine, Rifampicin

[a] ACEI: Angiotensin converting enzyme inhibitors; HMG: CoA: 3-hydroxy-3-methylglutaryl coenzyme A; NSAIDS: Non-steroid anti-inflammatory drugs.

generation DNA sequencing have tremendously improved our knowledge of the genetic basis of human disease, in general, and CVD, in particular. Cardiovascular pharmacogenomics is emerging as an important research field to unearth the genetic codes of cardiovascular DDI. Various common and rare genetic risk factors have been demonstrated in CVD, including the genetic variants associated with hypertension (Russo et al., 2018) and actin gene mutants in cardiomyopathy (Frustaci et al., 2018). The entire human genome has been already sequenced; >150,000 disease-related genetic variants have been mapped to >6000 Mendelian disorders (On-line Mendelian Inheritance in Man [OMIM]) (McKusick, 2007) and catalogued in the Human Gene Mutation Database (HGMD) (Stenson et al., 2017; Liang et al., 2017), which is useful for precision, personalized medicine (Leopold and Loscalzo, 2018). For example, a few gene variants are predictors of complex atherothrombotic CVD risk and severity. The interplays between genetic and environmental factors and drugs may predispose to resilience, i.e., the ability to adapt to insults from DDI adverse impacts. A recent study of 55,685 individuals reported that a polygenic risk score consisting of 50 single nucleotide polymorphisms (SNPs) is associated with a high genetic risk of coronary artery disease (CAD) and that the relative risk of coronary events decreases in those with a healthy lifestyle (Emdin et al., 2016, 2017; Khera et al., 2016a, 2016b).

Genome-wide association studies (GWAS) have been widely employed to genetically map disease association to genomic regions contributing to disease pathogenesis (Russo et al., 2018; Ross et al., 2004). GWAS support the concept that common, low-frequency, and rare variant complex disorders possess genetic heterogeneity. Several large consortia, including the International Consortium for Blood Pressure Genome-Wide Association Studies, Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE), Global BPgen, Wellcome Trust Case Control Consortium Studies, UK Biobank, PBCHARGE-EchoGen consortium, and CHARGE-HF consortium (Joshi et al., 2015; Locke et al., 2015; Shungin et al., 2015; International Consortium for Blood Pressure Genome-Wide Association et al., 2011), have identified >100 SNPs that affect BP. As a measure of functional utility, results of GWAS need to be integrated with phenotypic data, and generate Quantitative Trait Loci (eQTL). When one of such loci affects the expression levels of a

nearby gene located within 1 Mb from the coding sequence for the transcript, it is termed a cis-eQTL, and when an eQTL affects the expression levels of a more distal gene, it is called a trans-eQTL.

Disease susceptibility to drug treatment on a given genetic background may be defined by assessing an informative plethora of genes controlled by trans-eQTLs. Recent investigations reveal that about 30% of mammalian genes are controlled by eQTLs that heavily contribute to the susceptibility to complex diseases and/or DDI (Fehrmann et al., 2011; Westra et al., 2011). However, meta-analyses of GWAS data have failed to identify a single pathogenic gene specific for atherothrombotic vascular disease and myocardial infarction. The relationship between chromosome 9p21 and CVD, or more specifically myocardial infarction, has been proposed by several independent GWAS based on SNPs in 9p21 showing an associated increased risk of CVD (Sung et al., 2015). However, since SNPs are localized in the non-coding regions of chromosomes, and the nearest genes are >100 Kb away, the causality between SNPs and susceptibility to atherosclerosis remains uncertain.

DDI may occur with alterations in the toxicity, pharmacokinetics, or pharmacodynamics of two or more drugs when simultaneously applied (Koepsell, 2015; Palleria et al., 2013; Prueksaritanont et al., 2013). Genetic factors may contribute to the vulnerability to and impacts of DDI in patients with one or multiple diseases, largely through the regulation of the DDI biological responses. Genetic polymorphisms have been demonstrated in genes coding for drug metabolizing processes, including cytochrome P450 (Turner et al., 2020), or transporting proteins, such as p-glycoprotein (Holtzman et al., 2006) and organic cation transporter (OCT) (Zhou et al., 2021).

2.3. Cardiovascular drug interactome in association with therapeutic targets

Rapidly accumulating data from genomic and other panomic profiling research have revealed the existence of pharmacological "interactome" (*pharmacointeractome*) networks (Fig. 1) that function as regulators or determinants of multiple biological processes, in particular drug absorption, distribution, metabolism, transportation, and excretion, which not only coordinate to maintain the optimal dosage and duration of drug exposure to therapeutic targets, but also give rise to DDI (Palleria et al., 2013; Prueksaritanont et al., 2013). Physiologically and pathophysiologically, the expression of biological clock genes results in the temporal dimension of the drug interactome, leading to the administration-time, more properly circadian-time, dependent risk for DDI (Baraldo, 2008; Takahashi, 2017), as discussed in a subsequent section of this article in reference to hypertension therapeutics.

The cardiovascular drug-specific interactome may reside in the cardiovascular system or non-cardiovascular organs (e.g., liver and kidney). If established appropriately, the interactome can help dissect relationships between genes or proteins that may have broad applicability across a spectrum of different cardiovascular therapies. Such interactome networks may, therefore, constitute the basis for biologically relevant DDI at the levels of cells, organs, and whole body, which together contribute to the functions of the cardiovascular DDI pharmacointeractome. Assessment of the cardiovascular pharmacointeractome activity allows for unbiased and comprehensive consideration of multiple relevant genes, metabolites, and/or proteins that interplay during the development of a given cardiovascular pathological condition, such as atherosclerotic coronary heart disease (Turner et al., 2020) or hypertension (Russo et al., 2018; Luizon et al., 2018).

2.4. Cytochrome P450 (CYP) regulation of cardiovascular DDI

The cytochrome P450 (CYP) system (Nebert and Russell, 2002) consists of a large and diverse superfamily of hemoproteins with monooxygenase activity that participates in the metabolism and detoxification of both endogenous and exogenous substrates, including steroid hormones and drugs. CPY enzymes are probably the most important

Table 2

Examples of drug substrates, drug inhibitors, and drug inducers in cardiovascular DDI mediated by the different designated cytochrome P450 (CYP) enzymes.

Enzyme Name	Drug Substrates	Drug Inhibitors	Drug Inducers
CYP2C19	Clopidogrel, Propranolol, Warfarin	Moclobemide, Chloramphenicol, Many anti-convulsants (Valproate), Proton pump inhibitors (Omeprazole)	Rifampicin, Carbamazepine, Prednisone
CYP3A4	Donepezil, Statins (Atorvastatin), Ca-channel blockers (Nifedipine), Amiodarone, Dronedarone, Quinidine, PDE5 Inhibitors (Sildenafil), Kinins, Caffeine, Eplerenone, Propranolol, Salmeterol, Warfarin, Clopidogrel	Protease inhibitors (Ritonavir), Macrolides (Clarithromycin), Chloramphenicol, Nefazodone, Some Ca-channel blockers (Verapamil), Cimetidine, Some azole anti-fungals (Ketaconazole), Grapefruit juice	Some anti-convulsants (Carbamazepine), Baributrates (Phenobarbital), St. John's Wort, Some reverse transcriptase inhibitors (Efavirenz), Some Hypoglycaemics (Pioglitazone), Glucocorticoids, Modafinil
CYP2C9	Fluvastatin, Angiotensin receptor II agonists (Losartan), Warfarin, Torasemide	Some azole anti-fungals (Fluconazole), Amiodarone, Antihistamines (Cyclizine), Chloramphenicol, Fluvastatin, Fluvoxamine, Probenecid, Sertraline	Rifampicin, Secobarbital
CYP2D6	β-blockers (Propranolol), Class I anti-arrythmics (Flecainide), Donepezil	SSRIs (Fluoxetine), Quinidine, Sertraline, Terbinafine, Amiodarone, Cinacalcet, Ritonavir, Antipsychotics (Haloperidol), Antihistamines (Promethazine), Metoclopramide, Ranitidine, Mibefradil	Rifampicin, Dexamethasone, Glutethimide

elements of the oxidative and chemical modification of inactive pro-drugs into active therapeutic agents and also the degradation of drugs and other xenobiotics into inactive metabolites, accounting for up to 75% of the metabolism of medications, including those prescribed for coronary heart disease (Turner et al., 2020). However, the expected action of a given CYP enzyme can be inhibited by drugs or other chemical substances that simultaneously compete for access to it, thereby preventing the normal interaction between a drug and its metabolizing enzyme. Many cardiovascular drugs interact with other drugs via interference with the CYP enzymes (Benes et al., 2016; Shiota et al., 2008). Humans possess 18 families and 43 subfamilies of the CYP group of enzymes that target a variety of substrates. Certain CYP enzymes are particularly important in cardiovascular medicine because they impact cardiovascular drug substrates and DDI (Table 2). The activities of cardiovascular drugs can additionally be subjected to CYP-dependent interactions with certain consumed foods or liquids. For instance, alcohol abuse or misuse may affect CYP expression and function, particularly in the hepatic tissue, and grapefruit juice can inhibit the CYP3A enzyme leading to increased blood levels of atorvastatin and risk for adverse effects (Peluso et al., 2015; Kiani and Imam, 2007; Ando et al., 2005; Dahan and Altman, 2004; Kantola et al., 1998). Warfarin dose response is also highly regulated by the pharmacogenomics of CYP2C9 and VKORC1 (Yin and Miyata, 2007).

2.5. Circadian rhythm of cytochrome P450 in drug metabolisms

The constitutional clock genes and their complexes, through a predictable-in-time (circadian rhythmic) cycle, biologically activate or inactivate non-clock genes, resulting in the control and modulation of a great number of biological processes, including those that play a role in drug metabolism and transport (Zhao et al., 2020). These include ones that give rise to administration-time differences in the PK of drugs, i.e., their absorption from the gastro-intestinal tract, distribution in free and protein-bound form, metabolism, and/or excretion. It has been well documented that CYPs may function in a circadian rhythm fashion during human diseases and affect drug metabolism (Zhao et al., 2020; Kosir et al., 2013; Froy, 2009; Gachon and Firsov, 2011). Drug metabolism can be affected by circadian variation in the: (i) Phase I family of enzymes, which based on laboratory animal models collectively encompasses across different tissues at least 28 CYP450 entities; (ii) Phase II enzymes that modify Phase I-derived metabolites; and (iii) Phase III membrane transporters responsible for the elimination of the Phase II products. In combination, these circadian organized processes cannot only affect, sometimes substantially, the PK and pharmacodynamics (PD) of hypertension as well as many cardiovascular and other types of drugs according to the time of their ingestion or otherwise administration, but they also can give rise to the differential risk for DDI (Zhao et al., 2020; Kosir et al., 2013; Froy, 2009; Gachon and Firsov, 2011). Study of

drug-administration-time phenomena, with reference to the staging, e.g., peak and trough, of deterministic circadian rhythms, have resulted in new perspectives of the relationship between the PK and PD of medications (Reinberg et al., 1983). The absorption, distribution, metabolism, and/or elimination of a drug when dosed at different times during the 24 h, e.g., upon arising vs. at bedtime, can differ substantially. This is termed chronopharmacokinetics. The staging of circadian rhythms at the anatomical site or sites targeted by a given drug can be different from that which affect its PK, leading to a treatment-time-dependent disparity in the blood or tissue concentration-effect relationship that is not predicted by drug PK. This phenomenon is termed chronesthesy, a concept proposed by Reinberg et al. nearly 40 years ago (Reinberg et al., 1983). These and other concepts derived from the study of circadian rhythms and drugs (chronopharmacology) provide a novel perspective of administration-time differences in the behavior of cardiovascular and other therapies as well as novel insight into the mechanisms and manifestations of DDI. Therefore, the application of circadian rhythm-based investigative protocols is of critical importance not only to fully understand the PK and PD of single therapies when utilized at different times during the 24 h, but also the risk for DDI when several therapies are applied simultaneously (Hermida et al., 2021a).

3. Circadian rhythms as mediators of Cardiovascular DDI

This section introduces the concept of circadian timekeeping and its mechanisms, discusses the BP circadian rhythm and its specific features predictive of nonfatal and fatal CVD events, and reports the differential ingestion-time-dependent effects (relative to the staging of deterministic circadian rhythms) on the PK and PD of individual BP-lowering therapies as well as the vulnerability to DDI when such antihypertension therapies are used in combination.

3.1. Circadian clocks and timekeeping

At all hierarchical levels of organization, biological processes exhibit predictable-in-time variability expressed as endogenous-in-origin oscillations of specific period (τ), i.e., ultradian ($\tau < 20$ h, e.g., sleep stage cycles), circadian ($\tau \sim 24$ h, e.g., blood pressure, hormones, etc.), and infradian ($\tau > 28$ h, e.g., 28-day menstrual and 365 annual) domains, which together constitutes the biological time structure) (Halberg, 1969). *In vitro* and *in vivo* investigations have elucidated the molecular mechanisms of circadian timekeeping in mammals, which is of high relevance to medical care (Allada and Bass, 2021). Circadian rhythms derive from an endogenous central master biological clock – the suprachiasmatic nucleus (SCN) – situated within the hypothalamus that through autonomic, neuropeptide, endocrine, and other mediator signals coordinate subservient endogenous peripheral clocks of cells, tissues, organs, and systems (Takahashi, 2017). The molecular components of the

circadian clock of the nucleated cell entail several core clock genes – *Bmal1, CLOCK, Per^1, Per^2, Per^3, Cyr^1, Cyr^2, CLOCKp,^{er1}, per^2, Per^3, Cyr^1, and Cyr^2* – that generate autonomous intracellular circadian oscillations (Takahashi, 2017). The transcriptional activator complex of *BMAL1* and its partner *CLOCK* or *NPAS2* binds to the E-box elements in the promoter region of the *PER* and *CRY* repressor genes. Following translation and post-transcriptional modification, the PER and CRY proteins re-enter the nucleus as a congregated complex that acts to terminate their transcription, thereby closing the feedback loop, with the entire cyclic process requiring ~24 h to complete. Entrainment of most circadian rhythms to a period (τ) of exactly 24 h and also their staging, e.g., timing of the peak and trough values, of individual rhythms are mainly achieved through the sensing of cyclic environmental time cues, the primary one being the ambient 24 h light/dark cycle. Light cues perceived by the non-cone/non-rod intrinsically photosensitive melanopsin-containing retinal ganglion cells (ipRGCs) are conveyed via the retinohypothalamic neural tract to the SCN. The SCN through neural pathways controls the circadian rhythm of the synthesis of the hormone melatonin in the pineal gland. Melatonin is additionally cyclically inhibited and enabled, respectively, by the environmental light and dark 24 h cycle; accordingly, in humans melatonin circulates only during the darkness of nighttime, thereby constituting the biochemical messenger of environmental darkness, i.e., nighttime, to biological processes at all hierarchical levels. The totality of the rhythmic organization arising from the regulatory role of the circadian clocks of the genome (Lowrey and Takahashi, 2004), epigenome (Feng and Lazar, 2012), metabolome (Castro et al., 2015), proteome (Mauvoisin et al., 2014, 2015), and microbiome (Liang et al., 2014), comprises the circadian time structure (CTS) (Ballesta et al., 2017).

3.2. Blood pressure circadian rhythm

High BP, or hypertension, is one of the most common vascular disorders, highly prevalent in developed as well as developing countries, which often results in serious pathology of the blood vessels and heart, kidney, and other vital organs. Hypertension increases the risk for nonfatal and fatal CVD incidents [https://www.who.int/news-room/fact-sheets/detail/hypertension]. Systolic (S) and diastolic (D) BP (SBP and DBP) exhibit significant circadian variability (Hermida et al., 2001), and the PK and PD of antihypertensive therapies additionally exhibit significant circadian variability according to the time of their ingestion (Smolensky et al., 2010; Hermida et al., 2013, 2020a). BP displays a predictable activity/sleep temporal variation that derives from the interrelationship between the 24 h cycles of behavioral and environmental phenomena plus various circadian rhythms driven by the SCN-coordinated peripheral clocks, primarily neuroendocrine (noradrenaline and adrenaline of the autonomic nervous system [ANS], and prorenin, plasma renin, angiotensin-converting enzyme, angiotensin I and II, and aldosterone (renin-angiotensin-aldosterone system [RAAS]); endothelial, calcitonin gene-related, and other vasoactive peptides; atrial natriuretic; and hemodynamic factors (Smolensky et al., 2017a). Only around-the-clock ambulatory BP (ABP) monitoring (ABPM) – as opposed to wake-time office (OBPM) and home BP measurements – is able to assess and characterize the 24 h SBP and DBP pattern that is representative of the totality of these exogenous 24 h cyclic and endogenous circadian rhythmic factors (Hermida et al., 2015, 2017a; Smolensky et al., 2015a).

Large ABPM-based CVD outcomes investigations (Hermida et al., 2011, 2018a) have resulted in a novel definition of true arterial hypertension (Hermida et al., 2018b) and new tactics to optimize therapy for its clinical management (Hermida et al., 2007, 2016, 2017b, 2020b; Smolensky et al., 2015b, 2017b, 2020). These outcome trials plus various meta-analyses substantiate CVD events are much better predicted by the asleep BP mean than the conventional wake-time OBPM (Hermida et al., 2011, 2018a; Ben-Dov et al., 2007; Roush et al., 2014). Additionally, the relationship between the attenuated sleep-time relative SBP decline –

extent of SBP dipping, defined as the percent decrease in the mean SBP during sleep relative to the mean SBP during wake-time activity and calculated as ([awake SBP mean – asleep SBP mean]/awake SBP mean) x 100 – and increased CVD risk is well documented (Hermida et al., 2011, 2018a; Ohkubo et al., 2002; Salles et al., 2016). Thus, an elevated sleep-time SBP mean and blunted sleep-time relative SBP decline – non-dipper (sleep-time relative SBP decline <10%) or riser (sleep-time relative SBP decline <0%) 24 h SBP profile – not only constitute in combination the strongest joint predictor of CVD risk, independent of the wake-time OBPM or the awake or 24 h ABP means but important therapeutic targets for CVD prevention and prolongation of patient event-free survival (Hermida et al., 2007, 2011, 2016, 2017b, 2018a, 2018b, 2020b; Smolensky et al., 2015b, 2017b, 2020).

3.3. Treatment-time – circadian rhythm-dependent – differences in the PK and PD of drugs

Chronopharmacology is the study of biological rhythm influences on the PK and PD of medications, and chronotherapeutics is the timing of drugs to features of biological rhythms to optimize their therapeutic benefits and safety (Reinberg et al., 1983; Smolensky and Portaluppi, 1999). Currently, intense research in these fields is being pursed to improve the control of high BP to better prevent target organ pathology and to better attenuate CVD morbidity and mortality. The PK of oral BP-lowering (and other) medications can be significantly affected by foods; however, it also can be significantly affected by multiple endogenous circadian rhythms that affect their absorption, distribution, metabolism, and/or elimination (Baraldo, 2008; Bruguerolle, 1998). Studies show that the PD of therapies are not solely dependent on the rhythm-influenced PK but also different rhythms that affect the: (i) concentration of the circulating drug free-fraction and the receptor number/conformation and second messengers/signaling pathways of their cell/tissue targets, which for antihypertension medications include directly or indirectly the blood vessels of the general circulation and the heart, brain, and kidney tissues; and (ii) mechanisms precisely organized in time that regulate the 24 h BP pattern, particularly the ANS and RAAS (Smolensky et al., 2017a). Thus, it should not be surprising that the time, with reference to the staging of deterministic circadian rhythms, when BP-lowering drugs are ingested impacts the extent of the beneficial effect exerted in normalizing the 24 h BP profile of hypertension and also the risk for adverse effects (Hermida et al., 2021b, 2021c).

3.4. Ingestion-(circadian)-time-dependent differences in the effects of antihypertension drugs

As background to understanding the potential role of circadian rhythms in mediating hypertension DDI, it is first necessary to appreciate the extent to which the effects of BP-lowering medications of different classes and their combinations are affected by the time of their ingestion. We conducted a comprehensive review of the published literature on this topic (registered with PROSPERO – International Prospective Register of Systematic Reviews, no. CRD42020201220). Details of the search and meta-analysis of retrieved data, particularly regarding the main BP outcome variables most strongly associated with CVD risk, i.e., sleep-time SBP mean and sleep-time relative SBP decline, can be found elsewhere (Hermida et al., 2021b, 2021c).

3.5. Ingestion-(circadian)-time differences in the effects of antihypertension drugs applied as monotherapy

Among the retrieved 155 trials published between 1976 and 2020 that met all the inclusion/exclusion criteria, collectively representing 23,972 hypertensive individuals, 113 of them evaluated an oral BP monotherapy. Some 22 of these trials were "neutral", i.e., evidenced no ingestion-time difference in their therapeutic effects, while the other 91 (80.5%) trials demonstrated significantly enhanced BP reduction mainly

during sleep, moderation/reversal of the higher CVD risk non-dipper 24 h BP pattern, and/or greater beneficial effects upon the kidney and heart by the bedtime/evening treatment schedule. Quantitative evaluation of the data of the 62 randomized trials that utilized around-the-clock ABPM to assess the therapeutic effects substantiated the bedtime/evening vs. upon waking/morning treatment schedule resulted in statistically significantly better reduction of the asleep SBP mean by an average of 5.17 mmHg (95% confidence interval: [4.04, 6.31], P < 0.01 between treatment-time groups), but not the awake SBP mean (0.71 mmHg [-0.04, 1.46], P = 0.06), and it further increased the sleep-time relative SBP decline) by an average of 3.22% ([2.42, 4.02], P < 0.01) towards the normal dipper 24 h BP pattern. The augmented reduction of the asleep SBP mean by the bedtime/evening treatment schedule was greater for individuals at highest CVD risk, i.e., non-dipper (8.30 mmHg [6.39, 10.21], P < 0.01), diabetic, chronic kidney disease (CKD), and previous CVD-event patients (7.99 mmHg [3.03, 12.95], P < 0.01), than uncomplicated (absence of such diagnoses/medical history) lower CVD risk hypertensive patients (4.20 mmHg [3.09, 5.31], P < 0.01). Furthermore, *none* of the ABPM-based hypertension monotherapy trials reported the conventional morning-time treatment schedule to be more beneficial than the bedtime/evening treatment one; 51 (82.3%) of the 62 ABPM-based trials disclosed significantly enhanced advantages of the bedtime/evening schedule of treatment, while the other 11 (17.7%) trials showed non-inferiority of it in comparison to the morning one (Hermida et al., 2021b, 2021c).

3.6. Exploration of circadian rhythms as a mediator of antihypertension dual-combination therapy DDI

Traditional investigations of the pharmacogenomics and DDI of cardiovascular and other therapies in humans and in laboratory experiments on animal models have adhered to the principle of homeostasis that assumes relative constancy of the internal milieu. However, this major principle of pharmacology and medicine has often caused the misconception that biological processes and functions are rather invariable in time. Indeed, many previous trials of the efficacy and safety of medications and research of agonistic and antagonistic DDI have seldom addressed the potential influence of circadian or other biological rhythms in regard to when (e.g., during the day or night time) drugs are ingested or otherwise administered, and neither has the influence of circadian rhythms been taken into consideration in determining the sampling requirements of laboratory animal and human investigations to properly research pharmacointeractome networks.

Hermida et al. (2010a) apparently reported, for the first time, the relevance of the circadian time (using each subject's bed and awakening times as surrogate biomarkers of such) that a combination of anti-hypertension drugs is ingested as a cause of DDI. They randomized 203 ABPM-diagnosed hypertensive patients into one of four 160 mg valsartan/5 mg amlodipine dual therapy regimens: (i) both medications ingested upon awakening; (ii and iii) either one of them ingested upon awakening and the other at bedtime; or (iv) both ingested at bedtime. ABPM and wrist actigraphy (utilized to accurately determine the onset and offset of daytime activity and nocturnal sleep) were both concomitantly applied for 48 consecutive hours at baseline before and again after 12 weeks of treatment. As shown in Fig. 2, the reduction of the asleep SBP/DBP means was significantly better achieved in participants who simultaneously ingested valsartan and amlodipine at bedtime than in participants of the other three groups who followed different schemes of treatment (P < 0.001). Moreover, ingestion of the fixed-dose, dual-combination valsartan and amlodipine drugs at bedtime, rather than upon awakening, resulted in larger reduction of the asleep SBP/DBP means than the corresponding awake means as well as enhanced SBP dipping, jointly the strongest indicators of future risk for CVD events. The findings of this investigation are consistent with the conclusion that a very significant beneficial agonist DDI effect results when valsartan and amlodipine are ingested together at bedtime than that of in comparison to when they are administered together upon awakening.

4. Clinical aspects of DDI

The use of multiple drugs, or polypharmacy, is more likely to involve elderly patients, who more often have multiple medical conditions than younger patients (Turner et al., 2020). However, such polypharmacy can involve individuals of any age prescribed multiple drugs, including
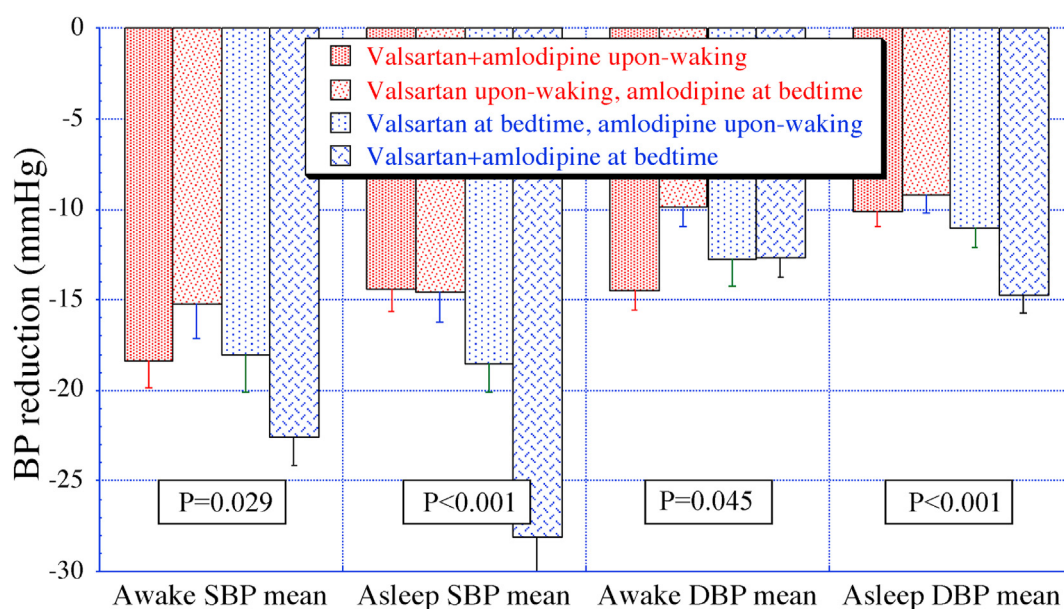

Fig. 2. Reduction (mmHg) of the 48 h ABPM-determined awake and asleep SBP and DBP means from baseline following 12 weeks of daily valsartan/amlodipine fixed-dose (160/5 mg/day) dual-combination therapy ingested by participants of comparable severity of hypertension (diagnosed according to guidelines-recommended ABPM thresholds) randomized to one of four groups, i.e., Group 1: both medications ingested upon awakening; Groups 2 and 3: either one of them ingested upon awakening and the other at bedtime; and Group 4: both medications ingested at bedtime. The depicted probability values obtained by analysis of variance of the data of the individual participants indicate the statistical significance of the difference in the effect of the four different valsartan and amlodipine ingestion-time schemes upon the awake and asleep SBP and DBP means.

so-called 'polypills' consisting of a combination of two or more therapeutic agents. Clinicians need to pay close attention to the medications and dosages they prescribe. For example, drugs that have a narrow therapeutic range, or a low therapeutic index, such as warfarin (Yin and Miyata, 2007) and 3-hydroxy-3-methylglutaryl co-enzyme A (HMG CoA) reductase inhibitors (e.g., statins) (Zhu et al., 2011; Yang et al., 2008, 2009, 2020), have the risk of severe DDI that can compromise both the safety and effectiveness of therapy. To avoid such undesired outcomes, it is important that cardiologists and other clinicians have proper knowledge of the multiple risk factors for CVD, such as age, gender, smoking, diabetes, hypertension, dyslipidemia, metabolic syndromes, depression, psychological stress, and other comorbidities, and a sufficient understanding of the potential risk of the prescribed polypharmacy for DDI as well as their management (Ferdinandy et al., 2014).

New therapeutic agents are continuously emerging, like biological and cellular ones (Madonna et al., 2016), that quickly become widely incorporated into clinical medicine to manage cardiovascular diseases. Drug interactions with cellular components or derivatives may occur when combination or multiple mono or dual therapies are applied. For instance, the HMG-CoA reductase inhibitors, statins, which are prescribed to lower blood cholesterol levels, are often used as an important constituent of the polytherapy of CVD patients. However, statins may exert their biological effects under the influence of circadian rhythm (see below). Simvastatin, for example, can block the expression of cytokine-induced nitric oxide synthase by inactivating the nuclear transcription factor NFκB (Madonna et al., 2005). In murine stem cells statin treatment also induces the expression of promyogenic genes and promotes stem cell differentiation into mature cardiac myocytes (Yang et al., 2014). Studies in a large animal infarct model (Yang et al., 2008, 2009; Xu et al., 2019; Song et al., 2013) and a human clinical trial (Yang et al., 2020) have demonstrated that preconditioning mesenchymal stem cells with atorvastatin improves stem cell survival, tissue repair, and regeneration of the lesions of myocardial infarction. On the other hand, there is a different expression in response to aspirin treatment of the epigenetic microRNA biomarkers of stromal mesenchymal stem cells of the myocardium versus epicardial adipose tissue (Ruan et al., 2020). The exploitation of multiple therapeutic interactions between cardiovascular and cellular or antibody treatments is emerging as an important topic of clinical DDI.

Cholesterol synthesis and absorption (Schroor et al., 2019), revealed by the plasma biomarkers of lathosterol, desmosterol, and mevalonic acid (Parker et al., 1984), that are indicative of HMG-CoA reductase activity, exhibits substantial circadian rhythmicity, with the greatest HMG-CoA reductase activity and cholesterol synthesis in the late evening and overnight. Presumably, this is the basis for the recommendation stated in the package insert accompanying the statin medications, e.g., simvastatin, lovastatin, prarastatin, and fluvastatin, that they be ingested in the evening (Smolensky et al., 2020). Likewise, other therapies commonly used by CVD patients should be preferentially recommended for a specific administration time. For example, multiple studies show once daily evening, compared with morning, low-dose (typically, 80–100 mg) aspirin (acetylsalicylic acid) therapy more markedly reduces the usual morning increase in COX-1-dependent platelet activity (Buurma et al., 2019; Bonten et al., 2014); also, evening, in comparison to morning, low-dose aspirin (100 mg) ingestion, exerts much better reduction of the awake, asleep, and 48 h DBP and SBP means, the effects being stronger in female than male patients with mild hypertension (Ayala and Hermida, 2010). Additionally, a series of recent publications based upon large cohort long-term follow-up trials report bedtime, compared to morning, antihypertension therapy substantially reduces the asleep SBP mean and enhances SBP dipping that translates into substantially better protection against the development of renal pathology and occurrence of CVD morbidity and mortality (Hermida et al., 2010b, 2020c).

Recently, a polypill formulation composed of 75 mg aspirin, 40 mg simvastatin, 10 mg lisinopril, and 12.5 mg hydrochlorothiazide was explored for administration-time differences of its therapeutic effects in a cohort of 78 CVD patients (Lafeber et al., 2015). Evening, rather than morning, ingestion of the polypill resulted in a small, but statistically significant (0.2 mmol/L [0.1 to 0.3]), lower fasting LDL-cholesterol level and non-statistically significant lower mean 24 h SBP (0.7 mmHg [-2.1 to 3.4]). However, the use of the 24 h SBP mean as the parameter for assessing the efficacy of hypertension therapy is improper because the SBP asleep mean and extent of asleep SBP dipping are much more strongly associated with CVD risk. Patients who have the same identical SBP mean can have a substantially different asleep SBP mean and dipping pattern and thus be at very different CVD risk (Hermida et al., 2021a). Very recently, the combination of bempedoic acid, ezetimibe, and atorvastatin has been shown to reduce LDL-cholesterol significantly in patients with hypercholesterolemia, based on a randomized phase 2 clinical trial (Rubino et al., 2021). It would be interesting to investigate in the future whether the efficacy of this combination therapy is affected by circadian rhythms, i.e., the time of its ingestion.

5. Conclusions

The first part of this article discussed and updated the conventional basic and clinical knowledge of the pharmacogenomics and pharmacointeractomes of cardiovascular DDI. The second part discussed the differential ingestion-time (using the bed and upon awakening times of the sleep/wake 24 h cycle as surrogate markers of circadian time) effects on both the PD of antihypertension monotherapies and the DDI of the fixed-dose dual combination valsartan-amlodipine therapy. To our knowledge, this is the first article to report when, i.e., the (circadian) time, multiple BP drugs are simultaneously ingested can be a deterministic factor of an agonist/synergistic DDI. Another type of potential adverse DDI effect in regard to the normally well-ordered CTS can be circadian disruption (Smolensky et al., 2016), i.e., disturbance of the normal patterning during the 24 h of the clock gene activities, resulting in alteration in the period and/or stage relationships between circadian rhythms at different hierarchical levels of biological organization, a condition much like the jet lag syndrome experienced by travelers when rapidly transported across multiple time zones by aircraft. Additionally, the findings presented here and elsewhere strongly support the hypothesis that the bedtime ingestion of mono and fixed-dose dual-combination hypertension therapies significantly better normalizes the asleep SBP mean and sleep-time relative SBP decline, and as beneficial consequence substantially offers better protection against pathology of the blood vessels of the kidney, heart, and other tissues, and most importantly CVD morbidity and mortality (Hermida et al., 2010b, 2011, 2016, 2018a, 2018b, 2020b, 2020c; Smolensky et al., 2015b, 2017b, 2020). They, thus, constitute additional evidence that the so-called bedtime hypertension *chrono*therapeutic scheme should be favored to optimally treat patients diagnosed with elevated BP.

It is hoped the knowledge conveyed here will optimize the outcomes of the polypharmacy of hypertension and CVD patients through increase of the safety and beneficial effects of therapy. A key goal of personized or precision medicine is the determination of the genetic and epigenetic factors that cause interactions between the multiple drugs of a patient's treatment regimen that can manifest either in adverse or altered beneficial effects. Past DDI research has focused on the conventional attributes of all of the involved therapies, such as their chemical composition, PK, dosage, and competing biochemical pathways of metabolism. Herein, we introduced an additional and novel dimension – circadian time – of the 'interactome' networks of DDI. Our comprehensive review of the published literature concerning circadian stage-dependent, i.e., administration-time, differences in the PK and PD of hypertension drugs reveals vast differences in the quality of the utilized research protocols, which motivated the development of guidelines for the high quality design and conduct of future investigations (Hermida et al., 2021a). Administration-time differences in the risk for and mechanisms of DDI are important areas of investigation but in need of agreed upon methods

and procedures to conduct such research.

There are important clinical implications of the information presented herein. Physicians, as usual procedure, should question patients about their lifestyle, especially the factors of exercise, diet, alcohol consumption, plus the use of over-the-counter medications, vitamins, nutritional supplements, and herbal remedies, since they may affect the actions and safety of prescribed therapies. Furthermore, they should consider the sex-related co-medication effects and appropriately address the interplay between the patient's gender (Perrino et al., 2021), CVD and its risk factors, co-morbidities, and associated co-medications (Ferdinandy et al., 2014). Understanding of the risk factors of patients for CVD and also knowledge of the risk factors for DDI of commonly prescribed cardiovascular therapies are critical in order for physicians take a more aggressive approach to improving the adherence of patients to multiple therapies as well as educating them to comprehend and recognize antagonistic and agonistic DDI.

Credit author statement

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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