Published in final edited form as:
Handb Exp Pharmacol. 2013 ; 217: 243–260. doi:10.1007/978-3-642-25950-0_10.

Molecular Clocks in Pharmacology

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Abstract

Circadian rhythms regulate a vast array of biological processes and play a fundamental role in mammalian physiology. As a result, considerable diurnal variation in the pharmacokinetics, efficacy, and side effect profiles of many therapeutics has been described. This variation has subsequently been tied to diurnal rhythms in absorption, distribution, metabolism, and excretion, as well as in pharmacodynamic variables, such as target expression. More recently, the molecular basis of circadian rhythmicity has been elucidated with the identification of clock genes, which oscillate in a circadian manner in most cells and tissues and regulate transcription of large sets of genes. Ongoing research efforts are beginning to reveal the critical role of circadian clock genes in the regulation of pharmacologic parameters, as well as the reciprocal impact of drugs on circadian clock function. This chapter will review the role of circadian clocks in the pharmacokinetics and pharmacodynamics of drug response, and provide several examples of the complex regulation of pharmacologic systems by components of the molecular circadian clock.

Keywords

circadian clock; pharmacology; pharmacokinetics; pharmacodynamics; CLOCK; Bmal1

1. Introduction

The maintenance of homeostasis is essential for all biological systems, and requires rapid adaptation to the surrounding environment. The evolution of circadian rhythms in mammals exemplifies this, as organisms have developed mechanisms for physiologic modulation to match the varying conditions dictated by a 24 hour light-dark cycle. An immense body of evidence over the past century has demonstrated that circadian rhythms influence most key physiologic parameters. More recently, the molecular machinery responsible for generating and maintaining circadian rhythms has been described, and it has become clear that these cell autonomous molecular clocks ultimately control organismal circadian rhythmicity, from endocrine function to complex behavior. Because circadian rhythms are so fundamental to mammalian physiology, it stands to reason that circadian physiologic variation would have significant implications for pharmacology. Indeed, many studies have demonstrated that circadian regulation plays an important role in both the pharmacokinetics and pharmacodynamics of many drugs. Cellular processes ranging from drug absorption to target receptor phosphorylation are influenced by the time of day and in many cases directly by the molecular circadian clock. As a result, circadian regulation can have substantial impact on the efficacy and side effect profile of therapeutics, and should thus be considered

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when developing drug dosing regimens, measuring drug levels, and evaluating drug efficacy. The resultant field of chronopharmacology is dedicated to understanding the time of day in pharmacology, and to optimizing drug delivery and design based on circadian regulation of pharmacologic parameters. In this review, we will briefly describe the molecular basis of the circadian clock, we will review studies demonstrating the impact of circadian rhythms on physiologic and pharmacologic parameters, and we will describe the molecular mechanisms by which the circadian clock influences pharmacologic targets. The goal of this review is to provide a framework within which to consider circadian influences on future investigations in pharmacology.

2. Molecular anatomy of the mammalian circadian system

The generation and maintenance of circadian rhythms in mammals depends both on a core molecular machinery, as well as a complex anatomical organization. As a result, circadian rhythmicity requires functional cell autonomous oscillation, neuroanatomical circuitry and neurotransmission, and paracrine and endocrine signaling systems. Circadian rhythms are maintained via the function of tissue-specific molecular clocks that are synchronized through communication with the master clock located in the suprachiasmatic nucleus (SCN) of the hypothalamus, which is entrained to light by an input from the retina (Reppert and Weaver 2002). The SCN synchronizes peripheral clocks in various organs to light input via regulation of diverse systems including the autonomic nervous system, pineal gland, and hypothalamic-pituitary axis. Nevertheless, isolated peripheral tissues and even cultured cells maintain circadian rhythmicity in the absence of input from the SCN (Baggs et al. 2009). The core molecular clock components responsible for this cell autonomous rhythmicity consist of “positive limb” components, Bmal1 and CLOCK, which are basic helix-loop-helix/PER-arylhydrocarbon receptor nuclear translocator-single minded protein (bHLH/PAS) transcription factors that heterodimerize and bind to E-box motifs in a number of genes, driving transcription (Reppert and Weaver 2002). Another bHLH/PAS transcription factor, NPAS2, which is highly expressed in the forebrain, can alternatively heterodimerize with Bmal1 to facilitate transcription (Reick et al. 2001; Zhou et al. 1997). Bmal1/CLOCK drive transcription of several distinct negative feedback (“negative limb”) components, including two Cryptochrome (Cry1,2) genes and three Period genes (Per1-3). Per and Cry proteins then heterodimerize and repress Bmal1/Clock-mediated transcription (Kume et al. 1999). Molecular clock oscillation is also influenced by two other Bmal1/CLOCK targets, RORα (retinoid-related orphan receptor alpha) and REV-ERBα. RORα bind to specific elements and enhances Bmal1 transcription (Akashi and Takumi 2005; Sato et al. 2004). REV-ERBα, another orphan nuclear receptor involved in glucose sensing and metabolism, competes with RORα for DNA binding and suppresses Bmal1 transcription (Preitner et al. 2002). The core clock machinery (referred to herein as the circadian clock) is found in most tissues and has been estimated to mediate the circadian transcription of roughly 10–20% of active genes (Ptitsyn et al. 2006).

Recent evidence has demonstrated that the regulation of the molecular clock periodicity is complex and subject to a wide array of influences. The circadian protein CLOCK has intrinsic histone acetyltransferase activity and can thus participate in epigenetic regulation of chromatin structure, and acetylation of other proteins, including molecular clock components (Doi et al. 2006; Etchegaray et al. 2003). Indeed, post-translation modifications of molecular clock proteins, including phosphorylation, SUMOylation, and acetylation, are critical for tuning of molecular clock function (Cardone et al. 2005; Gallego and Virshup 2007; Lee et al. 2001). Clock function is modified via input from diverse signaling proteins including casein kinase I epsilon (Akashi et al. 2002), the deacetylase SIRT1 (Asher et al. 2008; Belden and Dunlap 2008; Nakahata et al. 2008), the metabolic sensor AMP kinase (Lamia et al. 2009), and the DNA repair protein Poly-ADP ribose polymerase (Asher et al.

2010). Molecular clock function is also sensitive to the redox status of the cell (Rutter et al. 2001), and in turn regulates intracellular NAD+ levels through regulation of the enzyme nicotinamide phosphoribosyltransferase (NAMPT) (Nakahata et al. 2009; Ramsey et al. 2009). Thus, the molecular clock is sensitive to a wide array of physiologic (and pharmacologic) cues.

3. Circadian regulation of pharmacokinetics

Circadian systems have been shown to influence drug absorption, distribution, metabolism, and excretion (ADME). Each of these processes plays a role in determining blood levels on a drug. Thus, time of day of drug administration, as well as the synchronization of the peripheral molecular clocks in several key organs (including the gut, liver, and drug target tissue) can have substantial effect on drug levels and bioavailability.

3.1 Absorption

The absorption of orally-administered drugs depends on several factors including physiologic parameters of the GI tract (blood flow, pH, gastric emptying) and expression and function of specific uptake and efflux pumps on epithelial cell surfaces. Gastric pH plays an important role in the absorption of drugs, as lipophilic molecules are absorbed less readily under acidic conditions. Since the initial demonstration of circadian variation in gastric pH in humans by Moore et al in 1970, considerable evidence has accumulated showing the existence of circadian clocks within the gut, and the importance of these clocks in the timing of gut physiology (Bron and Furness 2009; Hoogerwerf 2006; Konturek et al. 2011; Moore and Englert 1970; Scheving 2000; Scheving and Russell 2007). The production of the hormone ghrelin by oxyntic cells in the stomach is regulated by circadian clock genes and mediates circadian changes in activity prior to feeding, known as “food anticipatory activity” (LeSauter et al. 2009). Oxyntic cells are thus tune the circadian oscillation of the GI tract to food intake patterns rather than light. Other gut parameters which show circadian oscillation include gastric blood flow and motility, both which are increased during daylight hours and decreased at night (Eleftheriadis et al. 1998; Goo et al. 1987; Kumar et al. 1986).

The absorption of many therapeutic agents is highly dependent on the expression of specific transporter proteins in the gut. Many of these transporters show circadian variation in expression, and several have been demonstrated to be directly regulated by the core circadian clock. In mice, the xenobiotic efflux pump Mdr1a (also known as p-glycoprotein) exhibits circadian regulation (Ando et al. 2005) which is controlled by the circadian clock-mediated expression of hepatic leukemia factor (HLF) and E4 promoter binding protein-4 (E4BP4) (Murakami et al. 2008). Several other efflux pumps, including Mct1, Mrp2, Pept1, and Bcrp, also show circadian expression patterns (Stearns et al. 2008). The circadian regulation of both physiologic parameters and the expression of specific proteins involved in drug absorption provide a mechanistic basis for understanding observed time-of-day effects in the absorption of many drugs. Circadian patterns of absorption are most pronounced in lipophilic drugs, with greater absorption occurring during the day than at night (Sukumaran et al.). Interestingly, absorption of the lipophilic beta blocker propranolol was significantly greater in the morning than at night, while the water-soluble beta blocker atenolol showed no significant diurnal variation in absorption (Shiga et al. 1993). While wild type mice show diurnal variation in lipid absorption, with greater absorption occurring at night, this diurnal variation was lost in CLOCK mutant mice. As a result, CLOCK mutants demonstrated significantly greater lipid absorption in a 24hr period (Pan and Hussain 2009). Several lipid transport proteins, including microsomal transport protein (MTP), are also regulated by the circadian clock in mice, suggesting that intestinal uptake of lipids and lipophilic drugs may be under circadian clock control in humans (Pan and Hussain 2007, 2009; Pan et al. 2010).

As a result of these diurnal variations in physiologic parameters and transporters/efflux pumps, the absorption on many drugs, including diazepam (Nakano et al. 1984), acetaminophen (Kamali et al. 1987), theophylline (Taylor et al. 1983), digoxin (Lemmer 1995), propranolol (Shiga et al. 1993), nitrates (Scheidel and Lemmer 1991), nifedipine (Lemmer et al. 1991), temazepam (Muller et al. 1987), and amitriptyline (Nakano and Hollister 1983), is sensitive to the time of day of administration. The absorption of most drugs is greater in the morning, paralleling morning increases in gut perfusion and gastric pH. Thus, circadian factors must be considered when developing oral therapeutic administration regimens.

3.2 Distribution

The volume of distribution of a given drug is determined largely by that drug's lipophilicity and plasma protein binding affinity, as well as the abundance of plasma proteins. Circadian regulation of the concentration of plasma proteins can thus theoretically induce circadian changes in the volume of distribution of a drug. Circadian regulation of plasma levels of several proteins which commonly bind drugs have been reported (Scheving et al. 1968). The degree of protein binding of several drugs, including the antiepileptic agents valproic acid and carbamazepine, and the chemotherapeutic cisplatin, varies in a diurnal manner which correlates appropriately with changes in plasma albumin level (Hecquet et al. 1985; Patel et al. 1982; Riva et al. 1984). Variations in the free (active) fraction of drug have important implications for both the efficacy and side effect profile of these drugs. Circadian variation in the levels and saturation of the glucocorticoid binding protein transcortin has also been described, which may influence the efficacy of exogenously administered corticosteroids (Angeli et al. 1978). As plasma protein levels influence the distribution of a wide array of drugs beyond those described here, it is likely that circadian regulation of these proteins has a significant impact on pharmacology.

The ability of a drug to cross membranes between different tissue compartments is also a determinant of drug distribution. Because many water soluble agents require the expression of certain membrane-bound proteins (transporters, channels) to transit between tissue compartments and reach their receptors, the circadian regulation of such transporter has implications for drug distribution. As described above in the section on absorption, a variety of drug transporters which are critical for drug distribution in tissues are regulated by circadian mechanisms (Ando et al. 2005; Stearns et al. 2008).

3.3 Metabolism

Hepatic metabolism of drugs generally occurs in two phases which are carried out by distinct set of enzymes. Phase I metabolism usually involves oxidation, reduction, hydrolysis, or cyclization reactions, and is often carried out by the Cytochrome P450 family of monoxidases. Phase II metabolism involves conjugation reactions catalyzed by glutathione transferases, UDP glucuronyl-, methyl-, acetyl-, and sulfo-transferases, leading to the production of polar conjugates which can be easily excreted. There is evidence of circadian regulation of both phases of drug metabolism.

Diurnal variation in the levels and activity of various phase I metabolic enzymes in the liver of rodents has been long appreciated (Nair and Casper 1969). Experiments in mice and rats have demonstrated that many Cytochrome P450 (CYP) genes show a circadian expression profile (Desai et al. 2004; Hirao et al. 2006; Zhang et al. 2009). Several non-CYP phase I enzymes also show diurnal variation. Recently, ample evidence has accumulated which shows that phase I metabolic enzyme expression is regulated by the circadian clock machinery (Panda et al. 2002). The core circadian clock exerts transcriptional regulation indirectly through circadian expression of the PAR bZIP transcription factors DBP, HLF,

and TEF, which in turn regulate expression of target genes. In mice, the expression of Cyp2a4 and Cyp2a5 demonstrated robust circadian oscillation and was shown to be directly controlled by the circadian clock output protein DBP (Lavery et al. 1999). In mice with targeted deletion of all three PAR bZIP proteins, severe impairment in hepatic metabolism was observed as well as downregulation of the phase I enzymes Cyp2b, 2c, 3a, 4a, and CYP oxidoreductase (Gachon et al. 2006). These mice also had diminished expression of a diverse array of phase II enzymes including members of the glutathione transferase, sulfotransferase, aldehyde dehydrogenase, and UDP-glucuronosyltransferase families. Similarly, microarray analysis of gene expression for the livers of mice with deletion of the circadian genes RORα and –γ revealed marked downregulation of numerous phase I and II metabolic enzymes (Kang et al. 2007). Thus, circadian transcriptional regulation of phase I genes has major implications for drug metabolism.

Phase II metabolism is also regulated by circadian mechanisms. Initial studies in mice demonstrated diurnal variation in hepatic glutathione-S-transferase (GST) activity, with greatest activity being present during the dark (active) phase (Davies et al. 1983). However, subsequent studies also observed circadian regulation of GST activity, but with the acrophase during the light (rest) period (Inoue et al. 1999; Jaeschke and Wendel 1985; Zhang et al. 2009). Diurnal variation in UDP- glucuronosyltransferase and sulfotransferase activites has also been described, which appeared to be dependent on feeding cues (Belanger et al. 1985). As mentioned previously, genetic deletion of the circadian output genes DBP, HLF, and TEF, or the circadian regulators RORα and –γ, caused large scale disruption of phase II enzyme expression in liver, suggesting a prominent role for the circadian clock in phase II enzyme regulation. The expression the aryl hydrocarbon receptor (AhrR), a transcription factor which mediates toxin-induced phase II enzyme induction, is also regulated by the circadian clock. Several studies have demonstrated that under AhR is under transcriptional regulation of the core circadian clock, and that AhR-mediated induction of Cyp1a1 by the AhR agonist benzo[a]pyrene is highly dependent on time-of-day of administration (Qu et al.; Shimba and Watabe 2009; Tanimura et al.; Xu et al.). Circadian regulation of hepatic blood flow has been suggested to regulate drug metabolism, particularly for drug with a high extraction rate (Sukumaran et al. 2010).

3.4 Excretion

Urinary excretion of metabolized drugs is highly dependent on factors related to kidney function. As diurnal variation in renal parameters including glomerular filtration rate, renal plasma flow, and urine output have been described, it is not surprising that diurnal variation in the urinary excretion of several drugs has been observed (Cao et al. 2005; Gachon et al. 2006; Minors et al. 1988; Stow and Gumz 2010). In mice, the circadian clock regulates the expression of several renal channels and transporter proteins, including epithelial sodium transporters, suggesting a possible direct role for clock genes in drug excretion (Gumz et al. 2009; Zuber et al. 2009). Circadian regulation of urinary pH could also contribute to variations in drug excretion, as many drugs become protonated at high pH which enhances excretion. Urinary pH shows diurnal variation in humans, perhaps explaining the diurnal variation in the excretion of certain drugs such as amphetamine (Wilkinson and Beckett 1968).

4. Circadian regulation of pharmacodynamics

Circadian mechanisms regulate many factors which influence the efficacy of drugs aside from their metabolism. Rhythmic alterations in the expression of target receptors, transporters and enzymes, intracellular signaling systems, and gene transcription all have been reported, and have the potential to impact the efficacy of therapeutics. While an extensive literature has emerged which examines the effect of various drugs on the phase

and rhythmicity of circadian clocks, there has been less emphasis on the effect of circadian clocks on drug targets. In the past, this work was largely limited to the description of diurnal changes in the levels of various receptors, enzymes, and metabolites, which suggested but could not prove circadian clock involvement. However, the recent development of an array of mouse genetic models with deletion or disruption of specific circadian clock genes has led to some initial discoveries demonstrating the pivotal role of the molecular clock in target function and drug efficacy. The chronopharmacology literature is extensive and often descriptive and an exhaustive account of the circadian regulation of all areas of pharmacology is beyond the scope of this review. Instead, illustrative examples from several areas of pharmacology will be presented. Circadian mechanisms play critical roles in cancer and chemotherapeutics, but because this topic is reviewed elsewhere in this volume, it will not be discusses herein. Similarly, the critical role of circadian clocks in cardiovascular pharmacology has been reviewed extensively elsewhere (Paschos et al. 2010; Paschos and FitzGerald 2010) and is not discussed.

4.1 Circadian clocks and neuropharmacology

The regulation of neurotransmitter signaling in the central nervous system is highly complex, and is the ultimate target of hundreds of drugs designed to treat a wide variety of disorders, from depression to Parkinson's disease. Ligand binding studies performed on mouse and rat brain homogenates have demonstrated time-of-day variation in the binding affinity of several neurotransmitter receptor families, suggesting possible circadian regulation of neurotransmitter signaling (Wirz-Justice 1987). Indeed, diurnal variation in radioligand binding which persists in constant darkness has been reported for α- and β-adrenergic, gabaergic, serotonergic, cholinergic, dopaminergic, and opiate receptors (Cai et al. 2010; Wirz-Justice 1987). The regulation of several enzymes involved in the catabolism of neurotransmitters also shows circadian variation in the brain (Perry et al. 1977a, b). As an example, the levels of monoamine oxidase A (MAO-A), which metabolizes catecholamines and serotonin and is a target of MAO inhibitor antidepressant drugs, are regulated by the core circadian clock (Hampp et al. 2008). Importantly, several of these same neurotransmitter systems, including serotonergic, cholinergic, and dopaminergic nuclei, also play critical roles in tuning the circadian clock. Thus, a bidirectional relationship between neurotransmitter regulation and circadian clock function exists in the brain (Uz et al. 2005; Yujnovsky et al. 2006).

Serotonin represents a particularly robust example of the bidirectional relationships between drugs and the circadian clock. Serotonin is a neurotransmitter which mediates a wide variety of effects in the central nervous system, but is perhaps most studied from a pharmacologic standpoint for its role in depression. Levels of serotonin show circadian rhythmicity in several brain regions, including the SCN, pineal gland, and striatum, which peaks at the light/dark transition and persists in constant darkness (Dixit and Buckley 1967; Dudley et al. 1998; Glass et al. 2003; Snyder et al. 1965). One reason for this is the fact that serotonin is converted to melatonin in the pineal gland during the dark phase by action of the enzyme serotonin N-acetyltransferase, which is expressed in a circadian manner (Bernard et al. 1997; Deguchi 1975). Circadian regulation of serotonin is dependent on input from the sympathetic nervous system, as adrenergic blockade or ablation of the superior cervical ganglion abrogated this diurnal rhythm (Snyder et al. 1967; Snyder et al. 1965; Sun et al. 2002). Diurnal variation in the serotonin transporter, the major target of selective serotonin reuptake inhibitors (SSRIs, the major class of antidepressant drugs), has been described in female rats, but no data exists for humans (Krajnak et al. 2003). A wide variety of antidepressant, anxiolytic, atypical antipsychotic, and antiemetic drugs target serotonin, either by increasing synaptic serotonin via inhibition of reuptake transporters, or by agonism or antagonism of specific serotonin receptors. Thus, the circadian regulation of serotonin

levels has implications for the dosing of these classes of drugs. Conversely, considerable evidence has accumulated in a variety of species showing that serotonin also plays a key role in regulating the circadian clock, as serotonergic signaling is required for normal SCN rhythmicity (Edgar et al. 1997; Glass et al. 2003; Horikawa et al. 2000; Yuan et al. 2005). Accordingly, drugs which modulate serotonin signaling have pronounced effects on circadian clock function. As an example, the selective serotonin reuptake inhibitor (SSRI) fluoxtine induces marked phase advances in SCN rhythms in mice (Sprouse et al. 2006). In a more global example, Golder et al. detected circadian rhythms in mood by analyzing millions of messages on the social networking website Twitter (Golder and Macy 2011). Mood peaked in the morning and declined as the day continued, and was consistent across diverse cultures. Thus, considerable circadian complexity must be considered when designing therapeutic strategies which target serotonergic systems.

4.2 Circadian clocks in metabolic diseases

Recent studies in genetically modified mice have revealed critical roles for circadian clock genes in metabolic diseases such as diabetes and obesity. Circadian clock genes regulate key metabolic processes such as insulin secretion, gluconeogenesis, and fatty acid metabolism (Bass and Takahashi 2010). A dominant negative mutation of CLOCK in mice results in obesity, hyperlipidemia, and diabetes (Marcheva et al. 2010; Turek et al. 2005). Bmal1/CLOCK heterodimers directly enhance transcription at the peroxisome proliferator response element, thereby contributing to lipid homeostasis (Inoue et al. 2005). Furthermore, expression of the nuclear hormone receptor peroxisome proliferator-activated receptor alpha (PPAR-α), the pharmacologic target of the fibrate drugs, follows a diurnal pattern in the liver which is abrogated in CLOCK mutant mice (Lemberger et al. 1996; Oishi et al. 2005). PPAR-γ, which is a major target of several anti-diabetes drugs including the thiazolinediones, is also under circadian transcriptional control of the clock-mediated PAR-bZIP transcription factor E4BP4 (Takahashi et al. 2010). Much like the serotonin system, PPAR-α and -γ also regulate the expression and function of circadian clock genes in a reciprocal manner (Canaple et al. 2006; Wang et al. 2008). Interestingly, a recent report demonstrated that the circadian clock gene Cryptochrome 1 (Cry1) blocks glucagon-mediated gluconeogenesis during dark phase (Zhang et al. 2011). The proposed mechanism of gluconeogenesis suppression by Cry1 was through suppression of G-protein coupled receptor (GPCR)-induced cAMP production. As cryptochrome genes are expressed in most tissue in a circadian manner as part of the core clock machinery, these findings have broad implications not only for metabolic disease therapy, but also for understanding the role of the circadian clock in the regulation of GPCR signaling in general (Zhang et al. 2011). As GPCRs represent the most common therapeutic targets in pharmacology, it appears likely that the influence of circadian mechanisms on pharmacodynamics is just beginning to be appreciated. Another emerging mechanism for the regulation of receptor signaling is acetlyation by molecular clock components. CLOCK has intrinsic acetyltransferase activity and can acetylate histones and other proteins (Curtis et al. 2004; Doi et al. 2006). Recently, it has been demonstrated that CLOCK acetylates the glucocorticoid receptor (GR), a nuclear receptor which is the target for exogenous glucocorticoids used to treat a wide variety of inflammatory diseases (Kino and Chrousos 2011a, b; Nader et al. 2009). CLOCK acetylates GR in a circadian manner, suppressing its activity and decreasing tissue sensitivity to glucocorticoids (Charmandari et al. 2011). This finding has broad implications for understanding endogenous cortisol regulation and the pharmacology of exogenous glucocorticoids in the treatment of disease, and may serve as a model for the regulation of other receptors by the circadian clock.

4.3 Aging, clocks, and pharmacology

Certain circadian rhythms, such as hormonal rhythms and sleep cycles, phase shift and then decline with age across species (Harper et al. 2005). In Drosophila, the function of the molecular clock is highly sensitive to oxidative stress, and dysfunction of the molecular clock is exacerbated by aging (Koh et al. 2006; Zheng et al. 2007). In mice and humans, expression of molecular clock genes declines and becomes dysregulated with age (Cermakian et al. 2011; Kolker et al. 2004; Nakamura et al. 2011; Weinert et al. 2001). Furthermore, deletion of Bmal1 or mutation of CLOCK in mice results in an accelerated aging phenotype, suggesting a bidirectional role of clock genes in aging (Antoch et al. 2008; Kondratov et al. 2006). The interaction between aging and circadian systems has several important implications for pharmacology. First, because circadian mechanisms influences nearly every aspect of pharmacology, the disruption of normal circadian function in elderly patients (as well as in shift workers, patients with chronic sleep disturbances, and others) is likely to have significant impact on drug efficacy and tolerance, and must be considered. Second, the impact of certain drugs on circadian clock function should also be considered in aged populations, as these patients are already likely to have some degree of clock dysfunction and may thus be more susceptible to drug-induced alteration in circadian rhythmicity. Finally, the circadian clock itself may become a therapeutic target for the amelioration of age-related diseases. Indeed, several studies have already demonstrated the feasibility of “clock drugs” which altered clock gene expression and rhythms (Hirota et al. 2010; Hirota et al. 2008).

5. Conclusions

Circadian biology influences nearly every aspect of physiology and pharmacology. Ongoing research has begun to unveil the molecular mechanisms by which circadian clock genes regulate pharmacokinetic and pharmacodynamic processes. It is also becoming readily apparent that drugs can influence the rhythmicty of circadian clocks and can potentially alter physiology, perhaps in some case with unintended consequences. Ongoing investigation into novel mechanisms by which molecular clocks alter pharmacologic parameters, the consequences of these alterations of on drug efficacy and tolerability, and possible methods to use circadian biology to our pharmacologic advantage is needed. At this point, it is clear that circadian regulation must be considered when designing and dosing drugs, particularly when therapeutic studies do not provide the expected results.

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