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Chronopharmacology: A New Approach and Overview

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Abstract

The majority of a mammal's physiology and behavior are time-dependent due to an innate "circadian" clock. Consequently, it is not unexpected that numerous facets of In pharmacology and medicine, the discovery of the biological clock has challenged some long-held beliefs and theories. The only way to cure diseases brought on by disruptions or dysregulation of the biological clock is to reset it. Numerous natural and lifestyle factors cause the clock to become deregulate. This review sheds light on the several chronotherapeutic medicines that have been identified and tested recently. The 24-hour clocks are also used to drive oscillations in toxicology and pharmacology.Circadian pharmacokinetics are based on daily fluctuations in the quantity of proteins required for medication absorption or metabolism; circadian pharmacodynamics are based on daily fluctuations in the physiological systems that these drugs target. The majority of bodily cells have these clocks, although they are arranged hierarchically. It's interesting to note that while some elements of physiology and behavior are directly regulated by a "slave" oscillator located in different brain areas or bodily tissues, others are regulated by a "master clock" located in the suprachiasmatic nuclei of the hypothalamus.

Key words: Circadian rhythms, chronopharmacology; drug delivery schedules; pharmacology; chronotherapeutic drugs drug metabolism, chronotherapy, cancer, peripheral oscillators, systems biology

Introduction

Living on a planet where the primary source of heat and light is only present occasionally, Earthly species had to quickly adjust their physiological systems to take advantage of these differences in order to maximize their fitness. The term "circadian" refers to all of these clocks collectively (Latin circa diem – approximately a day). All main organ systems in mammals are influenced by circadian clocks, and this influence directly affects disease pathology, which also varies with the time of day. In the past, rhythmic physiology has been linked to the symptoms of rhythmic diseases since ancient times. Around 400 BC, Hippocrates made the observation that whereas sleepiness during the day can be a sign of illness, insomnia at night might be a sign of discomfort. (1). There had been accounts of daily fluctuations in conditions such bronchial asthma by the Middle Ages. (2).

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It has been known for more than thirty years that people and rats have diurnal variations in medication distribution and absorption. For both humans and rats, a twenty-four-hour shift in medication bioavailability has been shown for hundreds of medicines. (3) Theophylline and acetaminophen, for instance, have distinct pharmacokinetic profiles in the morning and evening. These alterations are the outcome of multiple physiological and molecular changes that occur over time and affect how well drugs are absorbed and distributed. (4)

Life is rhythm; it cannot survive without it. The rhythms of breathing and heartbeat are necessary for life. The only biological function of our body is reproduction; all other processes have developed to support reproduction, which is the only way that life can continue. "Regular recurrence of quantities or accents of an event" is the definition of rhythm. Individuals are unable to reproduce (5) if their reproductive process becomes non-rhythmic. Males and females lack a reproductive cycle until adolescence, which prevents them from reproducing. Adults' circadian rhythms are regulated by estrogen receptor signaling in females. (6)

New Approaches For Drug Delivery Schedules

Rhythmic Notes

An arranged arrangement of notes is essentially what our ears perceive as music, in the same way that hormones secreted by endocrine glands work together to control the beat of reproduction. The pineal, hypothalamic, pituitary, testicles, and ovary glands make different hormones that interact in a certain and sequential way to control this essential bodily function. These glands are the notes in the reproductive rhythm. "Rhythmic Notes" pertains to the periodic trends found in the pharmacokinetics and pharmacodynamics of medications, together with the time-dependent impacts of drug delivery on biological functions, as documented in the field of chronopharmacology. (7)

Factors influencing the rhythms:

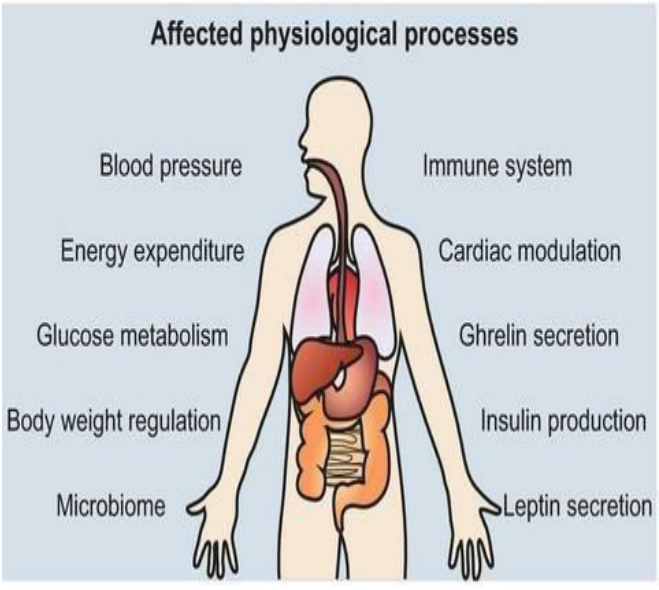
Environmental elements like light, temperature, altitude, radiation, and so on, as well as physiological factors like age, illness, and inheritance, have an impact on the nodes in the reproduction cycle. These elements regulate how the endocrine glands produce important hormones. For instance, light regulates the pineal gland's melatonin synthesis, which in turn regulates the sex cycle in both males and females.(8)

Aging and the clock

Age and insufficient daylight exposure cause circadian rhythms to gradually weaken and become disrupted. Alzheimer's disease (AD) is more likely to occur in older people, and AD further throws off circadian rhythms. Alterations in circadian rhythms, namely the sleep-wake cycle, heighten the neuropathological manifestations of Alzheimer's disease, including the build-up of amyloid-beta in the brain. This article describes the principles that underlie the normal age-related circadian rhythm modifications as well as the viscous cycle of disturbed circadian rhythms and the advancement of AD. (9)

Consequences in shift workers

The patterns of rest-activity, sleep-wake, and fasting-feeding are inexorably disrupted by shift work. Consequently, this might lead to sleep disorder and an internal circadian timing system that is not in sync with the outside world. Even though there is growing evidence that shift work negatively impacts metabolic and cardiovascular health, additional study is needed to identify and put into practice preventative and mitigating measures for these detrimental consequences.(10)



Chronotherapeutics

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Chronotherapeutics is the practice of treating a patient in accordance with their biological clock—daily, monthly, seasonal, or annual—to optimize positive health outcomes and reduce negative ones. (11) The scientific field of chronopharmacology studies how medications affect biological rhythms and events in time. Because of changes in biological processes The pathophysiology of several illnesses, including peptic ulcer disease, cardiovascular disorders, arthritis, asthma, and allergic rhinitis, causes symptom worsening over time. (12) Clock genes, specifically Per1, Per2, and Per3, are regularly expressed in the SCN and govern circadian rhythms, physiology, and behavior of mammalian bodies. Peripheral tissues also include the clock genes. Numerous genes in the liver display a circadian rhythm, according to recent experiments. The liver regulates daily physiological and biochemical activities and functions as a biological clock that can produce its own circadian rhythms. (13)

Experiments with blind

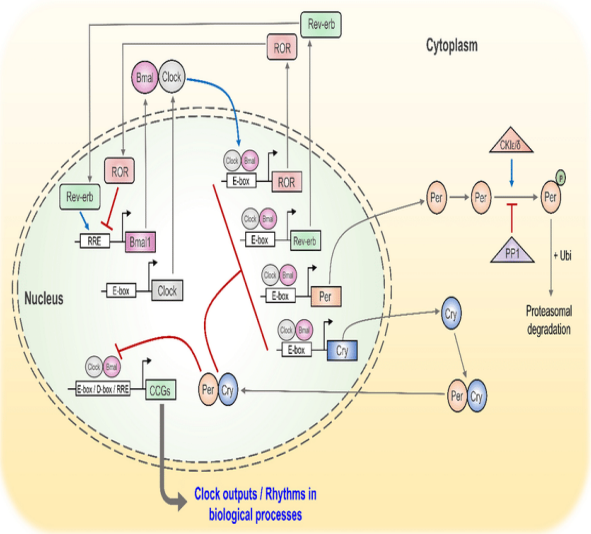
However, because light information cannot reach the hypothalamic circadian clock, the majority of blind individuals who are light-blind suffer from persistent circadian desynchrony. This leads to periodic bouts of restless nights and malfunction during the day. Since serotonin is converted to melatonin in the dark, they have consistently high blood levels of melatonin. Melatonin and its agonist, Tasimelteon, are safe and effective treatments for this disease; however, dosages need to be standardized. (14)

Drug Delivery

Certain medications release better in pulses; that is, when a drug is released as a "pulse" following a lag period, it must be planned so that the lag time is followed by a full and swift release of the drug. The duration that elapses between subjecting a dosage form to an aqueous environment and the onset of active component release from the dosage form is known as the lag time. Since the medicine produced by these systems is not affected by the surroundings, they are also known as time-controlled systems.(15)

Molecular Fundamentals of Circadian Clocks

A cell is the fundamental unit of circadian timekeeping; even in highly sophisticated animals, the majority of cells have independent circuitry for oscillations related to the circadian rhythm. This mechanism is essentially made up of negative feedback loops in transcription and translation: when a repressor gene is activated, its own protein product subsequently represses it. Because the repressor is unstable, this repression is ensured to be temporary, allowing for the start of a new cycle. The main players in this system in mammals are the homologs of the CLOCK and BMAL1 proteins, which dimerize and attach to cis-acting E-box elements (containing the straightforward consensus DNA sequence CAANTG) to trigger the transcription of several circadian genes. The PERIOD and CRYPTOCHROME families of repressor proteins (PER1-3 and CRY1-2), whose products multimerize and inhibit the CLOCK:BMAL1 activating complex, are encoded by loci found among these genes.(16)



An internal timekeeping mechanism called the circadian clock governs many physiological functions in living things, including humans, on an approximately 24-hour cycle. Deciphering the complex mechanisms that produce and sustain these rhythms at the molecular level is necessary to comprehend the molecular foundations of circadian clocks.(17)

From Circadian Control of Physiology to Chronopharmacology

As was previously mentioned, several aspects of cellular physiology, such as intracellular signaling cascades and transcription and translation, can exhibit diurnal fluctuations in activity. The diurnal physiological variation in most organ systems is

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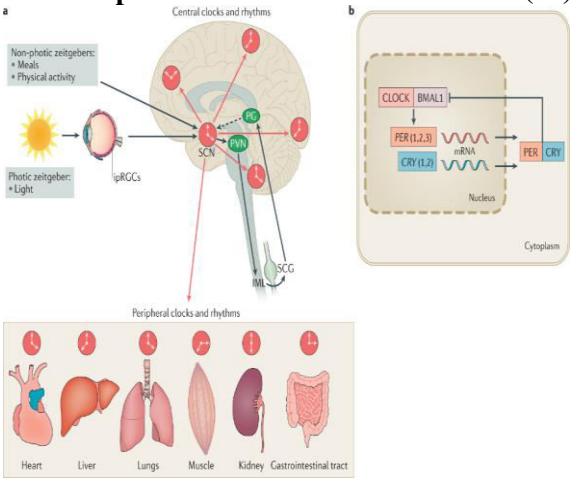
immediately translated into cellular variation, and this gives the molecular explanation for the circadian variation in PK/PD. (18)

Neurotransmitters and circadian behavior

Almost all behavior exhibits diurnal activity patterns. These oscillations have been demonstrated to occur most of the time regardless of the external environment or the sleep-wake cycle. Long-term memory, for instance, demonstrates a clear reliance on the circadian oscillator: mice with a functioning circadian system learn more effectively than those without, and both humans and rodents learn better at different times of the day.(19) Similarly, anxiety has a distinct daily pattern that is regulated by the circadian oscillator as well as sleep-wake cycles, and anxiety behaviors are increased in mice deficient in the Period clock gene. In both human and animal models, the experience of various **forms of pain exhibits diurnal variations. (20)**



Circadian hormones, cellular clocks, and the control of metabolism, digestion, and cardiac function

In addition to the neurotransmitters whose circadian production is either directly or indirectly controlled by the SCN, several additional hormones exhibit diurnal modulation that profoundly affects pharmacology and physiology. The pineal gland's circadian hormone, melatonin, affects local clocks in different parts of the brain in addition to influencing other aspects of retinal and cardiovascular function. (21)The adrenal gland's circadian rhythm causes the glucocorticoid hormone to be secreted during the day. This hormone has a significant impact on metabolism and is directly responsible for 60% of the liver transcriptome. Diurnal implications on digestive function are mediated via circadian modulation of somatostatin, ghrelin, and gastrin as well as direct regulation by autonomous clocks inside the gastrointestinal tract. More broadly, independent circadian clocks have a significant impact on physiology and metabolism in many different organs, including the GI tract. For example, local clockwork governs expression of various ion channels and kinases in the heart that impact cardiac function and lipid metabolism, and ablation of clocks in pancreatic islets causes diabetes due to abnormalities in coupling of β-cell stimulation to insulin production. (22) Recent transcriptome research has revealed extensive local circadian regulation in skeletal muscle, fat, and the heart, demonstrating that clocks in these tissues directly control physiology. (23)

Circadian immune regulation

The immune system is another well-known pharmaceutical target with robust circadian modulation. White blood cell counts and endotoxic shock susceptibility have long been known to fluctuate during the day. Nonetheless, current studies demonstrate that a wide range of circadian immunity characteristics are regulated by immune cells' own cell-autonomous clocks. For instance, T-cell responsiveness to stimulation fluctuates in a circadian manner, and macrophages, with their own internal clocks, elicit immunological responses in a similarly daily manner. (24)

Circadian Pharmacokinetics: Oscillations In Jejunal, Hepatic, And Renal Systems

Rhythmic gastric and intestinal absorption

Gastric pH controls drug ionization and hydrophobicity, which in turn affects drug transport and diffusion. The majority of animal species, including humans, have a circadian rhythm in their stomach pH, which affects how soluble drugs are. Additionally, gastrointestinal motility and post-meal stomach emptying occur at a faster rate during the day than at night, which contributes to increased absorption during the day. Interestingly, this rhythmic motility appears to be controlled by the circadian clock, at least for the colon, as animals without a clock have significant disruptions in this motility. Lastly, greater medication distribution over the day in humans

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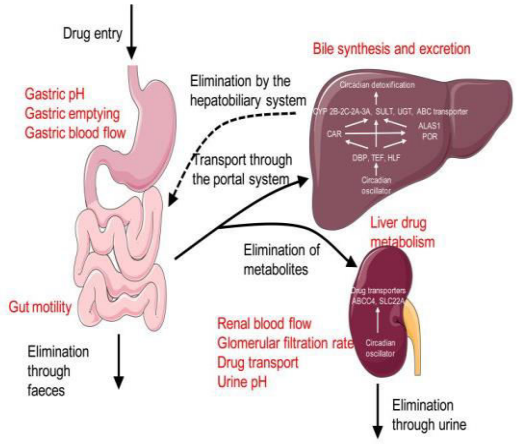
was also influenced by the gastrointestinal tract's higher blood flow in the morning. (25)



Rhythmic liver drug metabolism

The detoxification of xenobiotics is structured as a multi-step process made up of three protein groups that each perform different and sequential roles. Phase I proteins use the oxidase, reductase, and hydroxylase activities of the microsomal P450 cytochrome (CYP P450) family of enzymes to functionalize pharmaceuticals (maybe for inhibition or activation). (26) To improve solubility, phase II proteins conjugate pharmaceuticals to a hydrophilic molecule. They aid in the hydrophilicity of lipophilic substances, enabling easier excretion into bile, urine, and feces. Sulfotransferases, UDP-glucuronotransferases, glutathione S-transferases, and N-acetyltransferases are the primary enzymes responsible for achieving these reactions. Lastly, xenobiotics are transported outside of cells via phase III transporters, primarily ABC transporters. On the other hand, cellular import is carried out by transporters belonging to the solute carrier family (Slc). (27)

Rhythmic elimination by the hepatobiliary system

While the majority of medications that have undergone metabolism are ultimately eliminated as plasma and then urine, others are initially eliminated from the body through the hepatobiliary system and end up in the gut where they undergo further hepatic metabolism or fecal excretion. In addition to facilitating the production of bile, the hepatobiliary transport system is necessary for the removal of several endo- and xenobiotics, such as medications, phospholipids, and cholesterol. (28) A wide variety of liver-specific export mechanisms are involved, depending on the kind of molecule. Bile salts (BS) and organic anions that are not bile salts are excreted through ABC transporters to create bile. The conjugate export pump (MRP2 or ABCC2) excretes divalent BS and anionic conjugates of endo- or xenobiotics, whereas the bile salt export pump (BSEP or ABCB11) excretes monovalent BS. Phospholipid export channel MDR2 or ABCB4 facilitates the excretion of phosphatidylcholine (PC), which joins bile-forming substances like cholesterol and BS to form micelles. Drugs that are cationic metabolized are eliminated by the multidrug export channel, often known as ABCB1 or MDR1. The two-half transporter ABCG5/8 for cholesterol and the breast cancer resistance protein (BCRP or ABCG2) for anionic conjugates are examples of additional export pumps. (29)

Rhythmic elimination by the kidney

The kidneys remove the majority of medicines that are soluble in water or their metabolites through urine. The renal blood flow (RBF), glomerular filtration rate (GFR), urine flow, urine pH, which affects the degree of urine acidification, and the kidney's ability to reabsorb or secrete drugs across the epithelium are among the intrinsic variables that affect the rate of drug elimination in the urine. It's interesting to note that in various mammalian models, all of these variables exhibit circadian behavior. (30)

Chronobiological Implications For Drug Treatment

How much of the information discussed above has been used to successful medication interventions? Successful cases of chronotherapy are those with clear symptoms that change with the time of day. The best way to relieve symptoms of bronchial asthma is to treat the condition such that plasma levels are at their greatest during episodes of dyspnea. In a similar vein, blood pressure exhibits a prolonged trough during the night and a dramatic increase in the early morning, which crucially corresponds with the peak for cardiovascular events. (31) This variance is present in both healthy normotensive individuals and people with essential hypertension. For instance, the extended-release formulation of the L-type calcium channel blocker Verapamil allows

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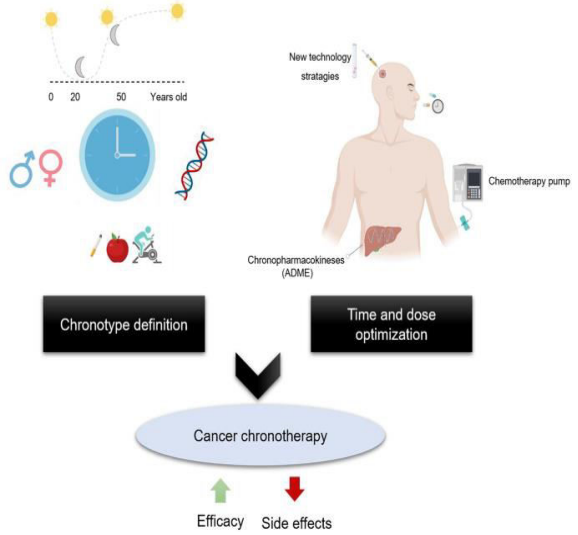
for therapeutically effective plasma levels in the early morning following oral treatment at bedtime. Furthermore, these delayed release medications have been advantageous for hypertensive individuals who do not exhibit a nighttime drop in blood pressure, a condition known as "non-dippers." Congestive heart failure is associated with non-dipping, even in individuals with clinically normal blood pressure. (32)

Cancer

In the case of chemotherapy and related cancer therapies, the predictions for the best treatment schedules become quite complex, whereas the chronotherapeutic approach in the aforementioned cases is based on comparatively few well-established variables. Chemotherapeutic doses should be strong enough to be toxic to the cancer, but low enough to avoid gravely harming healthy tissue or organs concurrently. Thus, pharmacokinetics and dynamics function within a limited therapeutic window. The numerous degrees of variation brought about by the circadian rhythm can be critical under these circumstances. The likelihood that the tumor has a clock in addition to the healthy tissue complicates matters further. This has been demonstrated in vivo by evaluating P32 incorporation in breast cancer tumors that are terminally sick. (33)



Implications for drug discovery and development

Traditionally, the confirmation of a target comes before the drug development process. The molecular targets are determined and the mechanism of action is established. Because the same experiments may need to be carried out at several different times of the day in order to determine whether, for example, a particular type of receptor or protein is only expressed at a specific time of day, taking into account the diurnal changes of relevant parameters could result in significantly higher costs. (34)On the other hand, one may search online for data about the circadian expression of a certain transcript or metabolite. In the search for medications to treat illnesses associated with aging, a unique situation arises. The rat species commonly employed in these tests have weaker circadian cycles, much like humans do. As a result, as people age, their PK/PD profile and target availability may alter. (35)

Conclusion

The latest research that we have highlighted provides light on the expanding subject of chronopharmacology as well as the molecular underpinnings of the PK/PD differences that have been noted in a great deal of cases. Still, a great deal of pertinent concerns remain unresolved. The majority, if not all, of the genomic circadian expression data used to draw these results are restricted to rodents. (36) It is not a given that these results may be applied to humans because drug transporters and metabolizing enzymes have very species-specific expression patterns and functional characteristics. Significant advancements in the characterisation of circadian variations in human protein expression and activity are imperative for the translation of research findings into therapeutic applications. (37)In the past, disorders caused by a malfunctioning biological clock were hard to cure. Pharmacology had no jurisdiction over these illnesses. However, when this clock was understood, it was able to control such disorders and provide patients with some comfort by developing some medications through the research of chronopharmacodynamics of certain chemical molecules. (38)

Despite the fact that the importance of the circadian clock on health, illness, and treatment has become much more well recognized in recent years, these discoveries do not appear to have been widely adopted by regulatory bodies or clinics. For the search word "circadian," there

have historically been 205 hits found in clinical trials databases that are accessible to the public, such as clinicaltrials.gov. Though none of them attempt to set up chronotherapeutic treatment regimens, twelve of them are connected to cancer. There are fourteen hits when "chronotherapy" is searched for. In comparison, 38331 items come up when you search for "cancer." Results from the EU clinical trials register were comparable. This seems excessive considering that over 20% of the transcriptome, proteome, and metabolome are controlled by clocks (39). Regarding regulatory bodies, the recommendations released by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) do not reference any of the chronobiological impacts on PK/PD that are described here. This is unexpected, especially in light of the fact that unanticipated hepatoxicity and cardiac adverse effects account for the majority of medication withdrawals from the market.(40)

References

1. Hippocrates, Laurentianus L, Galen . *Hippocratis medici Sententiarum particula prima[-septima]* Antonius Miscominus ex archetypo Laurentii … imprimi curauit; Florentiae: 1494. p. 196. (the first leaf blank) [Google Scholar]
2. Lemmer B. Discoveries of rhythms in human biological functions: a historical review. *Chronobiology international.* 2009;26:1019–68. [PubMed] [Google Scholar]
3. Kamali F, Fry JR, Bell GD. Temporal variations in paracetamol absorption and metabolism in man. *Xenobiotica; the fate of foreign compounds in biological systems.* 1987;17:635–41. [PubMed] [Google Scholar]
4. Watanabe H, Nakano S, Nagai K, Ogawa N. Time-Dependent Absorption of Theophylline in Man. *Journal of Clinical Pharmacology.* 1984;24:509–14. [PubMed] [Google Scholar]
5. Gupta, P.D. and Pushkala, K. (2012) Clocks within us LAMBERT Academic Publishing, GmbH & Co. KG, Saarbrücken, Germany. [PMC free article]
6. PD Gupta and K Pushkala. (2020) Clinical J Ophthalmology and Eye Care Review. [PMC free article]
7. Gupta P D Hormone Harmony, Publication Division CSIR, New Delhi, 1996. [PMC free article]
8. Pushkala, K. and Gupta,P.D. (2011) Dark side of the night light (Monograph) LAMBERT Academic Publishing, GmbH & Co. KG, Saarbrücken, Germany. [PMC free article]
9. Gupta, P.D. and Pushkala, K. J Anall Oncol, (2016), 146-152. [PMC free article]
10. https://www.sleep.theclinics.com/article/S1556-407X(15)00101 0/abstract [PMC free article]
11. Erkekoglu P, Baydar T. Chronopharmacokinetics of drugs in toxicological aspects: A short review for pharmacy practitioners. *J Res Pharm Pract.* 2012;1:3–9. [PMC free article] [PubMed] [Google Scholar]
12. Satwara RS, Patel PK, Shaikh F. Chronotherapeutical approach: Circadian rhythm in human and its role in occurrence and severity of diseases. *Int J PharmTech Res.* 2012;4:765–77. [Google Scholar]
13. Ohdo S. Chronopharmacology focused on biological clock. *Drug Metab Pharmacokinet.* 2007;22:3–14. [PubMed] [Google Scholar]
14. S W Lockley, M A Dressman et al.. Lancet P1754-1764, [2015] [PMC free article]
15. Usha Yogendra Nayak, Gopal Venktesh Shavi,et al J Controlled Release136(2) 125-131 [2009] [PMC free article]
16. Abraham U, Granada AE, Westermark PO, Heine M, Kramer A, Herzel H. Coupling governs entrainment range of circadian clocks. *Molecular systems biology.* 2010;6:438. [PMC free article] [PubMed] [Google Scholar]
17. Reischl S, Kramer A. Kinases and phosphatases in the mammalian circadian clock. *FEBS letters.* 2011;585:1393–9. [PubMed] [Google Scholar]

18. Kowalska E, Ripperger JA, Hoegger DC, Bruegger P, Buch T, et al. NONO couples the circadian clock to the cell cycle. *Proceedings of the National Academy of Sciences of the United States of America.* 2013;110:1592–9. [PMC free article] [PubMed] [Google Scholar]
19. Ruby NF, Hwang CE, Wessells C, Fernandez F, Zhang P, et al. Hippocampal-dependent learning requires a functional circadian system. *Proceedings of the National Academy of Sciences of the United States of America.* 2008;105:15593–8. [PMC free article] [PubMed] [Google Scholar]
20. Junker U, Wirz S. Review article: chronobiology: influence of circadian rhythms on the therapy of severe pain. *Journal of oncology pharmacy practice.* 2010;16:81–7. [PubMed] [Google Scholar]
21. Hardeland R, Cardinali DP, Srinivasan V, Spence DW, Brown GM, Pandi-Perumal SR. Melatonin--a pleiotropic, orchestrating regulator molecule. *Progress in neurobiology.* 2011;93:350–84. [PubMed] [Google Scholar]
22. Konturek PC, Brzozowski T, Konturek SJ. Gut clock: implication of circadian rhythms in the gastrointestinal tract. *Journal of physiology and pharmacology.* 2011;62:139–50. [PubMed] [Google Scholar]
23. Bray MS, Young ME. The role of cell-specific circadian clocks in metabolism and disease. *Obes Rev.* 2009;10(Suppl 2):6–13. [PubMed] [Google Scholar]
24. Keller M, Mazuch J, Abraham U, Eom GD, Herzog ED, et al. A circadian clock in macrophages controls inflammatory immune responses. *Proceedings of the National Academy of Sciences of the United States of America.* 2009;106:21407–12. [PMC free article] [PubMed] [Google Scholar]
25. Mendez-Ferrer S, Lucas D, Battista M, Frenette PS. Haematopoietic stem cell release is regulated by circadian oscillations. *Nature.* 2008;452:442–7. [PubMed] [Google Scholar]
26. Xu C, Li CY, Kong AN. Induction of phase I, II and III drug metabolism/transport by xenobiotics. *Arch Pharm Res.* 2005;28:249–68. [PubMed] [Google Scholar]
27. Gachon F, Fonjallaz P, Damiola F, Gos P, Kodama T, et al. The loss of circadian PAR bZip transcription factors results in epilepsy. *Genes and development.* 2004;18:1397–412. [PMC free article] [PubMed] [Google Scholar]
28. Trauner M, Wagner M, Fickert P, Zollner G. Molecular Regulation of Hepatobiliary Transport Systems: Clinical Implications for Understanding and Treating Cholestasis. *J Clin Gastroenterol.* 2005;39:S111–S24. [PubMed] [Google Scholar]
29. Duane WC, Levitt DG, Mueller SM, Behrens JC. Regulation of bile acid synthesis in man. Presence of a diurnal rhythm. *J Clin Invest.* 1983;72:1930–6. [PMC free article] [PubMed] [Google Scholar]
30. M, Takahashi Y, Komatsu R, Yamazaki F, Yamada H, et al. Salt-sensitive hypertension in circadian clock-deficient Cry-null mice involves dysregulated adrenal Hsd3b6. *Nat Med.* 2010;16:67–74. [PubMed] [Google Scholar]
31. Lago A, Geffner D, Tembl J, Landete L, Valero C, Baquero M. Circadian variation in acute ischemic stroke: a hospital-based study. *Stroke; a journal of cerebral circulation.* 1998;29:1873–5. [PubMed] [Google Scholar]
32. Hermida RC, Ayala DE, Mojon A, Fernandez JR. Blunted sleep-time relative blood pressure decline increases cardiovascular risk independent of blood pressure level--the "normotensive non-dipper" paradox. *Chronobiology international.* 2013;30:87–98. [PubMed] [Google Scholar]
33. Stoll BA, Burch WM. Surface detection of circadian rhythm in ^{32}P content of cancer of the

breast. *Cancer.* 1967;21:193–6. [PubMed] [Google Scholar]
34. Pizarro A, Hayer K, Lahens NF, Hogenesch JB. CircaDB: a database of mammalian circadian gene expression profiles. *Nucleic acids research.* 2013;41:D1009–13. [PMC free article] [PubMed] [Google Scholar]
35. Eckel-Mahan KL, Patel VR, Mohney RP, Vignola KS, Baldi P, Sassone-Corsi P. Coordination of the transcriptome and metabolome by the circadian clock. *Proceedings of the National Academy of Sciences of the United States of America.* 2012;109:5541–6. [PMC free article] [PubMed] [Google Scholar]
36. Martignoni M, Groothuis GMM, de Kanter R. Species differences between mouse, rat, dog, monkey and human CYP-mediated drug metabolism, inhibition and induction. *Expert Opin Drug Metab Toxicol.* 2006;2:875–94. [PubMed] [Google Scholar]
37. Dallmann R, Viola AU, Tarokh L, Cajochen C, Brown SA. The human circadian metabolome. *Proceedings of the National Academy of Sciences of the United States of America.* 2012;109:2625–9. [PMC free article] [PubMed] [Google Scholar]
38. Seán T. Anderson, Garret A. (2020) FitzGerald Sexual dimorphism in body clocks Science 369, (6508)1164-1165. [PMC free article]
39. Reddy AB, Karp NA, Maywood ES, Sage EA, Deery M, et al. Circadian Orchestration of the Hepatic Proteome. *Curr Biol.* 2006;16:1107–15. [PubMed] [Google Scholar]
40. Panda S, Antoch MP, Miller BH, Su AI, Schook AB, et al. Coordinated Transcription of Key Pathways in the Mouse by the Circadian Clock. *Cell.* 2002;109:307–20. [PubMed] [Google Scholar]

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