Pharmaceutical BIOPROCESSING

Pharmacology on Time

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Most people, if not all, have taken medicine prescribed as "once daily", rarely considering the time of day it is taken to be important. Even drug developers and doctors have been known to overlook time of dosage. Yet growing evidence shows that the timing is more important than previously thought for many medications. For instance, the time a hypertensive patient takes medicine may have a significant impact on the effectiveness [1].

Such timing effect is largely controlled by "circadian rhythm", one of the most notable and important biological rhythms in our bodies. Sleep/wake cycle, diurnal changes of blood pressure and morning surge of cortisol are among the best known circadian rhythms (Figure 1). The term circadian is derived from the Latin circa and die, meaning "around/about" and "day", respectively. Although circadian rhythm was believed to be generated by the external changes caused by the earth's rotation about 2.5 billion years ago [2,3], organisms evolved self-sustained mechanisms at a molecular level, letting rhythms persist even in the absence of daily environmental changes [4]. This rhythm is driven by a group of "clock genes" that are widely observed in animals, plants, bacteria, and even cultured cells [4]. In mammals, the core clock genes are rhythmically expressed in the suprachiasmatic nucleus, the central clock in the hypothalamus, as well as almost all peripheral tissues, where they control thousands of genes called clock controlled genes (CCGs) in a circadian manner, affecting various biochemical and physiological processes [5]. It has long been known that disruption of the circadian rhythms is a significant risk factor for the development of many prevalent diseases such as metabolic diseases, cardiovascular diseases, and sleep disorders [5]. Its disruption also suppresses our immune system and thus increases vulnerability to cancer and infectious diseases [6].

Because the circadian rhythms are so fundamental to physiology and health, it's not surprising that our body clock system has significant implications for pharmacology as well. However, the design of drug dosing is usually based on the assumption that the kinetic and dynamic change of the drug is constant throughout the day even if there are small diurnal variations. Many studies have demonstrated that the rate of drug absorption, distribution, catabolism, and excretion is circadian-time dependent, which reflects the substantial impact of circadian rhythms on drug efficacy and side effects [7]. Besides, the incidence and severity of many diseases, such as the onset of cardiovascular events, asthma, inflammatory diseases, and mental disorders display obvious temporal variations [5]. These drug and disease features have drawn increasing attention to the circadian clock. Accordingly, the word, Chronopharmacology (including chronopharmacokinetics and chronopharmacodynamics), was composed to describe the study of the relationship between drugs and biological rhythms, notably circadian rhythm.

The circadian clock system is not always dominating, but can be modulated by drugs, such as melatonin and modafinil that are used to treat circadian rhythm sleep disorders. In fact, more than half of the top 100 best-selling drugs in the United States target clock genes or CCGs [8]. However, most of them have not been associated with circadian rhythms and the influence of time of administration had not been taken into account during clinical trials. This reflects a fact that circadian effect is not a routine aspect of the examined features of most drugs. Given the intertwined interaction between circadian rhythms and pharmacological medications, it is expected that the timing of treatment in coordination with circadian clock would significantly increase the desired effects of drugs, decrease the tolerance, and minimize the toxicity. Therefore, circadian effect should be considered when developing drug-dosing regimens, particularly when therapeutic studies do not provide expected results.

Although the relationship between circadian rhythms and health has been extensively studied for a long time, the clock-drug interaction is not

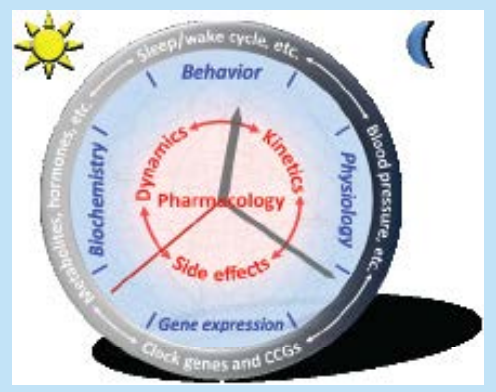

Figure 1: Pharmacological clock.

well investigated, especially in the translation of pharmacology from bench to bedside. We encourage researchers to continue contributing to our understanding of the clinical relevance of chronopharmacology. Chronotherapy has achieved good results in the treatment of cardiovascular diseases, asthma, depression, and inflammation. With more research, we hope to discover more effective treatments for more diseases.

References

1. Hermida RC, Ayala DE, Mojon A, Fernandez JR. Influence of circadian time of hypertension treatment on cardiovascular risk: Results of the MAPEC study. *Chronobiol. Int.* 27(8), 1629-1651 (2010).
2. Dvornyk V, Vinogradova O, Nevo E. Origin and evolution of circadian clock genes in prokaryotes. *Proc. Natl. Acad. Sci. U S A.* 100(5), 2495-2500 (2003).
3. Edgar RS, Green EW, Zhao Y, et al. Peroxiredoxins are conserved markers of circadian rhythms. *Nature*. 485(7399), 459-464 (2012).
4. Harmer SL, Panda S, Kay SA. Molecular bases of circadian rhythms. *Annu. Rev. Cell. Dev. Biol.* 17, 215-253 (2001).
5. Yang G, Paschos G, Curtis AM, et al. Knitting up the raveled sleave of care. *Sci. Transl. Med.* 5, 212rv3 (2013).
6. Scheiermann C, Kunisaki Y, Frenette PS. Circadian control of the immune system. *Nat. Rev. Immunol.* 13(3): 190-198 (2013).
7. Dallmann R, Brown SA, Gachon F. Chronopharmacology: New insights and therapeutic implications. *Annu. Rev. Pharmacol. Toxicol.* 54, 339-361 (2014).
8. Zhang R, Lahens NF, Ballance HI, Hughes ME, Hogenesch JB. A circadian gene expression atlas in mammals: implications for biology and medicine. *Proc. Natl. Acad. Sci. U S A.* 111(45), 16219-16224 (2014).