MOLECULAR CLOCK MECHANISM OF DRUG PHARMACOKINETICS
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Circadian rhythms have been observed in many biological systems and physiological functions. The effectiveness and toxicity of many drugs vary depending on the dosing time, associated with 24-hr rhythms of biochemical, physiological, and behavioral processes under the control of the circadian clock. Recently, several clock genes have been identified, and they control an array of circadian rhythms in physiology and behavior. According to the currently held model, the core circadian oscillator consists of an autoregulatory transcription-translation feedback loop (Fig). CLOCK and BMAL1 proteins form a heterodimer and then activate the transcription of Per and Cry genes. Once PER and CRY proteins have reached a critical concentration, they inactivate CLOCK:BMAL1-mediated activation of their own genes in a negative feedback loop.

Time-dependent changes in pharmacokinetics proceed from 24 hr rhythms in each process, e.g. absorption, distribution, metabolism and elimination. Since the liver is a major organ of metabolism and detoxification, knowledge of circadian effects on transcriptional activities that govern daily biochemical and physiological processes in the liver may play a key role in toxicology. In mouse liver, circadian regulation of transcripts is demonstrated for the factor of phase I, II of drug metabolism such as Cyp17, Cyp2a4, Cyp2e1, Cyp2c22, Cyp3a, glutathione S-transferases (GST) and carboxylesterase so on. In the recent our study, the transactivation of the human CYP3A4 gene by DBP is repressed by the E4 promoter-binding protein-4 (E4BP4), a negative component of the circadian clock (Fig). On the other hand, hepatocyte nuclear factor-1 alpha (HNF-1α) and clock genes contribute to produce the 24-hr rhythm of CYP2e1 mRNA levels in mouse liver. These findings support the concept that choosing the most appropriate time of day to administer the drugs associated with metabolic rhythmicity may be increasing the efficiency of pharmacotherapy.

References: