Synopsis of Original Research Paper

Molecular clock mechanisms of transporter and metabolic enzyme and the manipulation of biological rhythm

Shigehiro Ohdo

Department of Pharmaceutics, Graduate School of Pharmaceutical Sciences, Kyushu University

Mammalians circadian pacemaker resides in the paired suprachiasmatic nuclei (SCN) and influences a multitude of biological processes. Clock genes are the genes that control the circadian rhythms in physiology and behavior. Not only disease but also the effectiveness and toxicity of many drugs vary depending on dosing time. Identification of a rhythmic marker for selecting dosing time will lead to improved progress and diffusion of chronotherapy. The mechanisms underlying chronopharmacological findings should be clarified from viewpoint of clock genes. On the other hand, several drugs have an effect on molecular clock. Furthermore, to produce new rhythmicity by manipulating the conditions of living organs appears to lead to the new concept of chronopharmacotherapy. The knowledge of interactions between molecular clock and drug should be very useful for the clinical practice. In the present study, we demonstrated the circadian rhythm of CYP and transporter transcription in mice and in vitro cell culture system. Then we clarified the regulatory mechanisms underlying the rhythmicity of CYP and transporter transcription from viewpoints of molecular clock. Furthermore, we produced new rhythmicity by manipulating the conditions of living organs or culture cell by using rhythmic administration of altered feeding schedules or serum shock. The monitoring of rhythm and manipulation of rhythm from viewpoints of molecular clock are essential to improved progress and diffusion of chronopharmacotherapy. Therefore, we show the regulatory system of biological rhythm from viewpoints of clock genes and the possibility of chronopharmaceutics based on molecular clock.