Periodic variation in bile acids controls circadian changes in serum uric acid levels via regulation of hepatic expression of xanthine oxidase in mice

Satoru Koyanagi, Takumi Kanemitsu, Yuya Tsurudome, Naoki Kusunose, Masayuki Oda, Naoya Matsunaga, Shigehiro Ohdo

Pharmaceutics/Glocal Healthcare Science, Kyushu University, Japan

Xanthine oxidase (XOD), also known as xanthine dehydrogenase, is a rate-limiting enzyme in purine nucleotide degradation, which produces uric acid. Uric acid concentrations in the blood and liver exhibit circadian oscillations in both humans and rodents; however, the underlying mechanisms remain unclear. In this study, we demonstrated that XOD expression and enzymatic activity exhibited circadian oscillations in the mouse liver. The orphan nuclear receptor peroxisome proliferator-activated receptor- α (PPAR α) transcriptionally activated the mouse XOD gene and that bile acids suppressed the XOD transactivation. The synthesis of bile acids is known to be under the control of circadian clock, and we observed that the time-dependent accumulation of bile acids in hepatic cells interfered with the recruitment of the co-transcriptional activator p300 to PPAR α , thereby repressing XOD expression. This time-dependent suppression of PPAR α -mediated transactivation by bile acids caused an oscillation in the hepatic expression of XOD, which, in turn, led to circadian alterations in uric acid production. Finally, we also demonstrated that the anti-hyperuricemic effect of the XOD inhibitor febuxostat was enhanced by administering it at the time of day before hepatic XOD activity increased. These results suggest an underlying mechanism for the circadian alterations in uric acid production and also underscore the importance of selecting an appropriate time of day for administering XOD inhibitors.