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Effect of pharmacological enhancement of circadian clock in chronic kidney disease.

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Objectives: Recently, it has been demonstrated that the molecular clock system plays an important role in kidney diseases, and modulation of the molecular clock machinery is an attractive therapeutic target with a novel mechanism of action. Here, we optimized a substance that enhances the circadian molecular rhythm and validated its effect in chronic kidney disease (CKD).

Methods: In the CKD model, mice were fed a 0.25% adenine diet for 2 weeks, and drug treatment was started 1 week after the CKD was established.

Results: First, total RNA sequencing of CKD kidney tissue was performed to extract the top 50% genes whose expression was significantly increased. We found that 19% genes of the CKD-associated genes were rhythmically expressed in a circadian manner, and gene enrichment analysis of these genes revealed that they were associated with fibrosis regulation pathway, suggesting that alterations in circadian system during CKD may contribute to fibrosis progression. Next, based on the structure-activity relationship data of circadian enhancer, the formulation for in vivo application was optimized, and conditions under which the pharmacological mechanism to work effectively in kidney were established by combining PEG and Tween-80. Finally, when the optimized circadian enhancer was administered to adenine-induced CKD mice for 8 weeks, increased renal inflammation (TNF-a, IFN-r, IL-12, iNOS) and cell cycle arrest/senescence in CKD kidney were ameliorated, and renal function and fibrosis were significantly improved. Further molecular works are currently underway with in vitro experiments to understand the mechanisms of drug effects in CKD.

Conclusions: This is the first study to show that CKD progression is significantly attenuated when a novel small substance that enhances circadian rhythms is administered to CKD mice.
A better understanding of the complex role of the circadian clock in kidney diseases may provide new perspectives for the development of novel therapeutic strategies for CKD.