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CIRCADIAN RHYTHMS

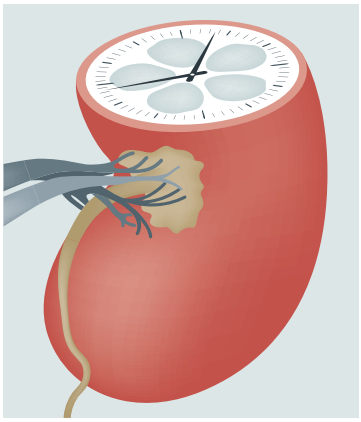
Functional roles of the renal tubular circadian clock

> In humans, dysfunctional circadian rhythms have been linked to hypertension and accelerated progression of chronic kidney disease

Circadian rhythms are regulated by a central clock mechanism in the hypothalamus that coordinates subsidiary clocks with cell-specific functions in the peripheral tissues. New data from Dmitri Firsov and colleagues suggest that the circadian clock of renal tubular cells controls various homeostatic and metabolic processes, including drug disposition.

"The circadian timing system controls many — if not all — specific renal functions," explains Firsov. "In humans, dysfunctional circadian rhythms have been linked to hypertension and accelerated progression of chronic kidney disease. However, the roles of the intrinsic circadian clocks located in renal cells remain largely unknown."

To investigate the roles of circadian clocks in the nephron, the researchers generated mice with conditional tubule-specific knockout of *Bmal1*, which Firsov describes as "the sole indispensable element of the circadian clock machinery". They report that these mice had no obvious renal abnormalities and their glomerular filtration rates and circadian patterns of renal water, sodium and potassium handling were similar to those of controls. The knockout mice did, however, show a small but statistically significantly decrease in systolic blood pressure and increases in plasma creatinine and urea levels compared with controls, suggesting an impairment of tubular function.



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Deep sequencing of the renal transcriptome identified alterations in the expression of genes with roles in metabolic pathways and organic anion transport in the knockout mice. The renal NAD^+:NADH ratio of these mice was also significantly decreased, indicating increased anaerobic glycolysis and/or decreased mitochondrial function. Moreover, metabolome profiling identified significant differences between the plasma levels of amino acids, biogenic amines, acylcarnitines and lipids in the knockout and control mice. "Collectively, these results indicate that the intrinsic tubular circadian clock controls a variety of metabolic and homeostatic processes at both the intrarenal and systemic levels," says Firsov.

Finally the researchers report that the knockout mice had significantly reduced expression of the organic anion transporter OAT3, which has a role in the tubular secretion of creatinine and various drugs, including furosemide. Consistent with this finding, the mice showed an impaired natriuretic response to furosimide and a reduced rate of urinary elimination of this drug compared with controls. The researchers conclude that similar to circadian clocks in the liver and intestine, renal circadian clocks have a role in drug pharmacokinetics.

"The kidney is composed of >20 highly differentiated cell types, which equate to >20 intrinsic renal circadian clock systems," says Firsov. "Thus we hypothesize that the circadian clock systems in different renal cell types may have distinct functional roles. Our next step will be to characterize the role of the circadian clock in glomeruli by performing a podocyte-specific knockout of the circadian clock system."

Ellen F. Carney

ORIGINAL ARTICLE Nikolaeva, S. *et al.* Nephron-specific deletion of circadian clock gene *Bmal1* alters the plasma and renal metabolome and impairs drug disposition. *J. Am. Soc. Nephrol.* http://dx.doi.org/10.1681/ASN.2015091055 (2016)