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POSSIBLE INVOLVEMENT OF BLADDER PERIPHERAL CLOCK IN THE CIRCADIAN CONTROL OF VOIDING FUNCTION

Hypothesis / aims of study

Circadian clocks are the endogenous oscillators that harmonize a variety of physiological processes within the body. Although many urinary functions exhibit clear daily or circadian variation in diurnal humans as well as in nocturnal rodents, the precise mechanisms of these variations are as yet unclear.

Study design, materials and methods

We examined daily water intake and urine excretion in young adult WT and *per1 per2* double knock-out (PDK) mice as 1 h or 2 h bins. Then we examined clock genes expression in the bladder (urothelium, detrusor smooth muscle and sphincter muscle), spinal cord (lumbar 4-5) and local brain regions related to micturition function (pontine micturition center, ventrolateral periaqueductal gray and medial preoptic area) by real-time RT-PCR. Finally using *Per2::Luc* knock-in mice, we monitored *Per2* promoter activity in whole bladders or bladder slices.

Results

We observed daily/circadian variations of water intake and urine excretion in a functional clock-dependent manner. Interestingly in PDK mice, water intake and urine excretion displayed arrhythmic pattern under constant darkness with significantly increased amount consumed and excreted when compared with those of WT mice. Moreover, we observed distinct oscillation of clock genes expression in the bladder and spinal cord. Finally, we observed that adult and neonate mouse bladders display clear and sustained oscillation of *Per2* promoter activity *in vitro*.

Interpretation of results

These results indicate that local circadian clocks reside in the bladder and may play important roles in the circadian control of micturition function. The first progress has been made in understanding the circadian mechanisms of micturition and roles of the circadian clocks in the context of various urologic conditions.

Concluding message

Possible roles of bladder peripheral clock in the voiding function and dysfunction are currently under investigation and further studies remain for the development of novel targets and appropriate situation-dependent adjustments for the treatment of nocturia.

Disclosures

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