RENAL DENERVATION

Sa001 \textbf{KIDNEY-SPECIFIC CLOCK MACHINERY COUPLED WITH DISTURBED CIRCADIAN RHYTHM OF BLOOD PRESSURE AND URINARY SODIUM EXCRETION IN NEPHROPATHY RATS}

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Introduction and Aims: Abnormal circadian rhythm of blood pressure (BP) is presented in chronic kidney disease. However, the mechanisms of disturbed BP rhythm remain elusive. We aim to establish the nephrotic syndrome model with abnormal BP rhythm and explore underlying mechanisms revolved with disturbance of the self-sustained circadian timing system of tubular sodium transporters.

Methods: Male Sprague-Dawley (SD) rats were intravenously injected with Adriamycin (ADR) as the nephropathy rats group. Others were injected equal dose of saline as the control group. The telemetry systems were implanted in five rats in each group for continuously monitoring parameters of the systolic arterial pressure(SAP), diastolic arterial pressure (DAP), mean arterial pressure(MAP), pulse pressure (PP) and heart rate(HR) every minute during 72 hours. The urines in Dark and Light period were collected synchronously for analysis the rate of urinary sodium excretion. Three adriamycin-induced nephrotic syndrome rats and three SD control rats were sacrificed every four hours throughout a 24-hour day-night cycle to determine the mRNA expression of clock genes Bmal1, Per1, Per2 and clock controlled genes NHE3, αENaC, NCC in the kidney.

Data were analysed by a partial Fourier analysis and a stepwise regression technique.

Results: There is no significant difference in average levels of 24 hours SAP, DAP and MAP between two groups. The control rats showed the higher BP in dark time (active period) than their BP in light time (rest period), while neither of the dark-light BP differences was statistically significant in ADR nephropathy rats. In the control group, rats exhibited the normal circadian rhythm with the urinary volume and the rate of urinary sodium (RUNa) in Dark period higher than those in Light period. However, in ADR rats RUNa in Dark period significantly lower than that in the Light period \([14.69 ± 3.65] \mu\text{mol/h} \text{ vs } [27.66 ± 5.84] \mu\text{mol/h}, P=0.001\), and significantly lower than that in the Dark period of control group \([14.69 ± 3.65] \mu\text{mol/h} \text{ vs } [39.49 ± 22.44] \mu\text{mol/h}, P=0.023\). On the other hand, our results demonstrated that clock genes Bmal1, Per1, Per2 and clock controlled genes NHE3, αENaC, NCC mRNA expression in kidney tissue of SD rats showed circadian pattern \((p<0.05)\), and the peak times of the expression rhythm of the genes were in the dark time, while the ADR nephropathy rats showed no significant circadian oscillating in those genes expression.

Conclusions: We characterized the ADR nephropathy rats lost the circadian rhythm of blood pressure coupled with the disturbance of urine sodium excretion rhythm compared with the SD control rats. We further demonstrated the ADR nephropathy rats lost the rhythm of the clock genes expression in the kidney which was conservative and stable in SD control rats. The kidney-specific clock-controlled genes for tubular sodium transporting of NHE3, αENaC, NCC expression pattern were also disturbed in ADR rats, while all these genes exhibit normal circadian patterns in SD control rats. To our knowledge, this is the first demonstration of the disturbance at molecular level of self-sustained circadian timing system in nephropathy rat. Kidney-specific clock machinery coupled with disturbed circadian rhythm of blood pressure and urinary sodium excretion in nephropathy rats. It is likely to prove useful in unraveling the role of clock system in renal disease.