Circadian Rhythms in Voiding Function and Dysfunction

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While circadian rhythms in fluid intake, urine production, and urine storage have been substantiated in diurnal human and nocturnal rodents, the mechanism(s) underlying it is largely unknown. With the elucidations of molecular clockwork and its functional significance in mammals, new opportunities arise to investigate possible circadian control of voiding function and dysfunction, which undoubtedly needs immediate attentions of researchers in the field.

Keywords: Voiding; Circadian; Clockwork; Sleep; Diurnal

Life on this rotating planet is confronted with periodic changes of its environment. Often, these changes are quite predictable like daily variations in environmental illumination, temperature, humidity, and food/predator availability. From an evolutionary perspective, organisms that can predict environmental changes and actively prepare themselves for these changes would have selective advantages over those who cannot. Indeed, endogenous mechanisms called circadian clocks have successfully emerged so that virtually all living things on Earth display circadian rhythms in their biochemistry, physiology, pathology, and behavior [1,2].

Consequently, most physiological functions are tightly locked to their activity/rest phases to ensure optimal performance. Day-active animals including humans consume most of their food during the day, while night-active animals like laboratory rodents during the night. Accordingly, water intake, urine production, and urine storage also display distinct circadian variations in diurnal human and nocturnal rodents. Intuitively, urine production and voiding must predominate during the active phase, whilst increased storage of urine in the bladder and reduced frequency in urination have to be ensured to promote better rest and sleep, which has been substantiated by research observations [3,4]. Moreover, failures of this homeostatic

regulation are predicted to negatively affect organisms' well-being. Indeed, nocturia (bothersome waking-up at night to void) are known to decrease quality of life and negatively affect morbidity and mortality in human beings, especially in the elderly [5,6]. Researches also indicated that nocturia disrupts sleep architecture and predicts obstructive sleep apnea while acute sleep deprivation results in excess diuresis and natriuresis [7,8].

Despite the ample evidence supporting clear circadian/diurnal variations in urine production and storage, the mechanism(s) underlying it is largely unknown. Now that molecular components of circadian clock have been identified and several mutant animal lines lacking in clock functions are available [1], novel approaches are needed to delineate whether voiding function and dysfunction are under the direct control of mammalian time-keeping system. This can be addressed by comparing clock-intact animals with those deficient either systemically or tissue-specifically in clock functions. In these efforts, key molecules linking circadian clock and voiding function should be clarified. Given the multifaceted nature of voiding function and dysfunction [5,9], however, all the possible alternatives need to be considered as well.

Since neural and humoral outputs of the suprachiasmatic nucleus (SCN), the master clock in mammals [10], orchestrate

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peripheral clocks present throughout the body, micturition centers in the brain [11] and local urinary functions in the kidney and bladder can be direct targets of circadian oscillator-driven hormones and neural activities. In addition, possible local clocks residing in the kidney and bladder may derive time of day-dependent urinary functions.

One crucial thing that should not be forgotten in designing experiments and interpreting their results is that we humans are diurnal while experimental model animals used in most urological researches are nocturnal. While a few similarities (i.e., increased neural activities of the SCN during the daytime and melatonin secretion during the night) are observed, lots of neuroendocrine and behavioral functions are completely reversed in diurnal and nocturnal mammals [12].

Considering that urological problems are one of the major complaints of the elderly in this aged society, and that lots of workers in the developed and developing countries are subjected to various shift work scheduling and circadian disruption, possible circadian controls of voiding function and dysfunction is undoubtedly an urgent agenda that requires immediate attentions of the researchers in the field.

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