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Circadian regulation of renal function

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Urinary excretion of water and all major electrolytes exhibit robust circadian oscillations. The 24-h periodicity has been well documented for several important determinants of urine formation, including renal blood flow, glomerular filtration, tubular reabsorption, and tubular secretion. Disturbance of the renal circadian rhythms is increasingly recognized as a risk factor for hypertension, polyuria, and other diseases and may contribute to renal fibrosis. The origin of these rhythms has been attributed to the reactive response of the kidney to circadian changes in volume and/or in the composition of extracellular fluids that are entrained by rest/activity and feeding/fasting cycles. However, numerous studies have shown that most of the renal excretory rhythms persist for long periods of time, even in the absence of periodic environmental cues. These observations led to the hypothesis of the existence of a self-sustained mechanism, enabling the kidney to anticipate various predictable circadian challenges to homeostasis. The molecular basis of this mechanism remained unknown until the recent discovery of the mammalian circadian clock made of a system of autoregulatory transcriptional/translational feedback loops, which have been found in all tissues studied, including the kidney. Here, we present a review of the growing evidence showing the involvement of the molecular clock in the generation of renal excretory rhythms.

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Circadian rhythms in renal function have been studied since the middle of the nineteenth century. In 1861, Edward Smith, one of the pioneers in circadian physiology, published the first documented evidence for the existence of circadian oscillations in renal excretion of urea and water.[1] (For an excellent historical review tracing the early stages in the development of the experimental chronobiology see Lavie[2].) Later studies showed that sodium, potassium, chloride, and other major electrolytes also follow circadian excretory patterns. Because most of the excretory rhythms are maintained in kidney transplant patients,[3] it was concluded that either humoral factors or yet unknown intrinsic renal mechanisms (or both) are involved in their generation. Analysis of circulating factors revealed that blood levels of vasopressin, aldosterone, and many other hormones responsible for maintaining water and electrolyte balance exhibit circadian oscillations.[4,5] Until recently, it was thought that these hormonal rhythms are entrained principally by circadian changes in the volume and/or composition of extracellular fluids produced by the rest/activity and feeding/fasting cycles. The evidence for the existence of an intrinsic renal mechanism remained elusive because of the difficulty in dissociating this mechanism from the effects of circadian circulating factors. The discovery of the circadian timing system allowed major advance in the understanding of the origin of renal excretory rhythms. Several recent studies have clearly shown that at least a part of the hormonal rhythms can be attributed to a self-sustained mechanism driven by the circadian clock at the site of synthesis and/or release of these hormones (see below). It was also shown that the kidney itself possesses an intrinsic circadian clock potentially involved in transcriptional/translational control of thousands of genes of the renal transcriptome.

CIRCADIAN CLOCK

The great majority of physiological processes run with a periodicity of ~24 h. The ~24 h period length gave rise to the name *circadian*, which is composed of two latin words *circa* (about) and *dies* (day). Functionally, circadian rhythms are thought to provide an important advantage by allowing the organism to anticipate the upcoming environmental changes. The molecular basis of circadian rhythms in mammals was uncovered at the end of the twentieth century. It was shown that the mammalian circadian clock is a hierarchically organized system of individual cellular oscillators

orchestrated by a self-sustained central pacemaker residing in the suprachiasmatic nucleus (SCN) of the hypothalamus (reviewed in Schibler *et al.*[6]). The SCN pacemaker is synchronized with the external world, primarily by the light/dark cycle. Its activity imposes the feeding pattern through the control of the rest/activity cycle. The feeding time is thought to be the dominant time cue for resetting circadian oscillators in peripheral tissues. However, the latter are capable of sustaining circadian rhythms for long periods of time in the absence of the SCN synchronization, thus showing a high degree of autonomy. Central and peripheral oscillators share a similar core clock based on a system of autoregulatory transcriptional/translational feedback loops composed of the transcriptional activators *Clock*, *BmalI*, and *Npas2*, and of the feedback repressors *Cry1*, *Cry2*, *Per1*, and *Per2* (Figure 1). Circadian oscillations of the core clock entrain circadian rhythms in expression of output genes, which are, in turn, translating these transcriptional oscillations into tissue-specific functional rhythms. Current estimates indicate that up to 10% of all genes are under the control of circadian transcriptional factors.

ROLE OF MOLECULAR CLOCK IN THE HOMEOSTATIC CONTROL OF WATER AND ELECTROLYTE BALANCE BY THE KIDNEY

Water

It is well established that the rate of urine formation by the kidney follows a well-defined circadian rhythm with a maximum excretion that takes place during the activity phase. This excretory pattern has been shown to persist for several days when activity/feeding cycles are either completely reversed or when water and meals are taken at regular intervals throughout the 24-h period.[7] On water restriction, the volume of excreted water is rapidly decreased and cycles disappear, thereby reflecting domination of the reactive mechanism of water conservation over anticipatory circadian functional rhythms. Urinary output of water depends on several parameters including circulating vasopressin levels, variations in the osmotic pressure along the corticomedullary axis, the renal blood flow (RBF), and the glomerular filtration rate (GFR). Hence, self-sustained circadian oscillation of one of these factors or their combinations would be capable of entraining circadian rhythms in water diuresis. Circadian variations in both RBF and GFR are well documented. Moreover, it has been shown that both RBF and GFR are oscillating in-phase with rhythms of urinary excretion of water and several major electrolytes.[8] However, the self-sustained rhythmicity has only been shown for the GFR.[9] Whether the corticomedullary osmotic gradient is following a circadian profile remains unknown. Data concerning circadian variations in blood vasopressin concentration remain limited owing, in part, to the low circulating levels of this hormone. A few available data indicate that maximal vasopressin levels are reached at the beginning of the activity phase.[10] Vasopressin is synthesized in the SCN, paraventricular, and supraoptic nuclei of hypothalamus. Significant circadian changes in vasopressin mRNA and protein abundance have only been detected in the SCN, in which about one-third of neurons synthesize this hormone.[11,12] The SCN-derived vasopressin is considered one of the major rhythmic outputs of the central pacemaker, which is involved, among other functions, in the control of hypothalamo–pituitary axis. Hence, it was proposed that oscillations in the SCN-derived vasopressin might be involved in the circadian release of this hormone from the posterior pituitary.[13] This interesting theory, however, requires further investigation.

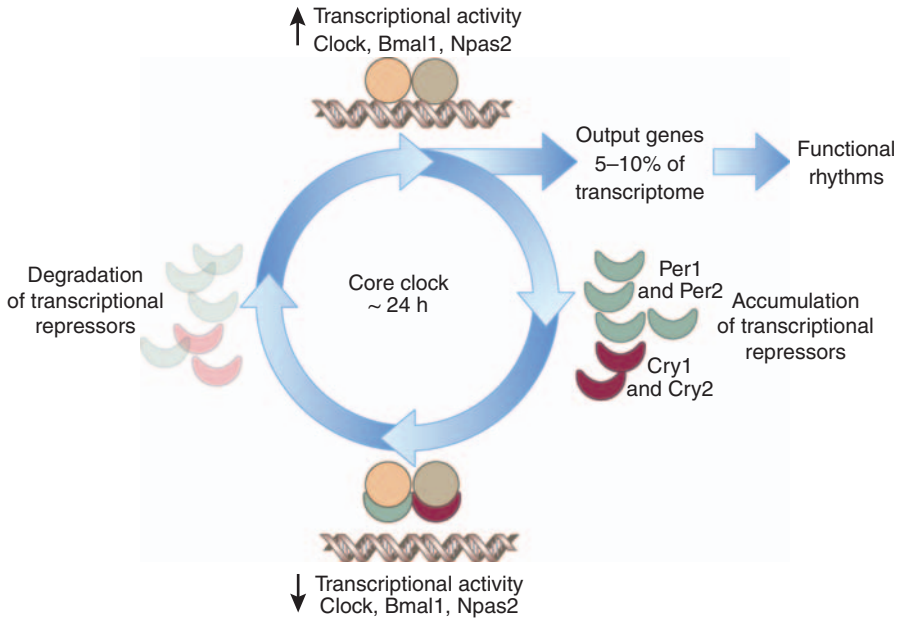

Figure 1 | Schematic presentation of circadian molecular clock.