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Commentary for Development of the Circadian Clockwork in the Kidney: Molecular Origin of the Kidney Clock

Michelle L. Gumz^{1,2,*}

¹Department of Medicine, Division of Nephrology, Hypertension and Renal Transplantation
University of Florida

²Department of Biochemistry and Molecular Biology University of Florida

Abstract

Increasing evidence suggests that a functional circadian clock in the kidney contributes to the regulation of renal function including blood pressure and sodium balance. When does this kidney clock begin ticking? Meszaros et al. provide the first evidence that the endogenous molecular machinery of the circadian clock begins oscillating in the late fetal kidney. These findings have important implications for our understanding of how homeostasis is maintained in early life.

The circadian clock is an intrinsic timekeeper that has evolved in order to synchronize the internal, rhythmic physiological processes of an organism with its external environment. The molecular machinery of this clock is expressed in nearly every cell type and tissue that has been tested and can be found in organisms ranging from archaebacteria to humans¹. The pacemaker of the circadian clock resides in the suprachiasmatic nucleus (SCN) of the brain where it is entrained by light cues that travel from the retina to the SCN via the retinal hypothalamic tract. This central clock in turn synchronizes the peripheral clocks located in other regions of the brain and in tissues such as the kidney and liver via neuronal and humoral signaling. Although most peripheral clocks can function autonomously, the central clock is thought to act as a conductor that guides the circadian orchestra of peripheral oscillators (reviewed in ¹).

The circadian clock begins ticking early in life. Indeed it has been known for some time that the clock oscillates in the fetal brain ². This presents an interesting concept in which the intrinsic clock of the fetus responds to the internal clock of the mother, and may then be synchronized to the mother's external environment. Recent studies have shown that fetal clocks exist in other tissues as well, including the liver, adrenal gland, and the colon ^{3,4}. In this issue, Meszaros et al. demonstrate for the first time that an intrinsic fetal and neonate kidney clock exists (Meszaros et al. *Kidney International* 2014).

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*Correspondence to: Michelle L. Gumz, Ph.D. University of Florida 1600 SW Archer Rd Box 100224 Gainesville, FL 32610 (P) 352-273-6887 (F) 352-392-5465 Michelle.Gumz@medicine.ufl.edu.

At a basic level, the molecular circadian clock consists of a core group of transcription factors that participate in a transcription translation oscillating loop (Figure 1). In the positive loop, Bmal1 and Clock heterodimerize and interact with E-box response elements in the promoters of target genes. Two of these target genes are the circadian proteins Period (Per, isoforms 1, 2, and 3) and Cryptochrome (Cry, isoforms 1 and 2). Per and Cry feedback on and inhibit the activity of Bmal1/Clock, thus inhibiting their own transcription. These core circadian clock proteins function in nearly every cell type and tissue that has been tested. It is estimated that at least 10% of expressed genes are regulated in a rhythmic manner in a given tissue and thus the list of circadian target genes is rapidly growing. The elegant report by Meszaros and colleagues in this issue includes the observation that several core clock elements exhibit rhythmic variations and that there is a role for nutritional cues in the entrainment of the fetal kidney clock (Meszaros et al. *Kidney International* 2014). They also demonstrate that kidney specific circadian target genes oscillate as early at embryonic day 20 (E20)(Figure 1, inset). Specifically, Sgk1, α ENaC, NHE3, and Avpr2 were expressed in a circadian manner. These genes have previously been identified as circadian target genes in the adult rodent kidney^{5, 6} but Meszaros et al. provide the first evidence that these genes, which encode proteins critical in the maintenance of water and sodium balance by the kidney, are early molecular targets of the circadian machinery. This finding is a key concept of the study in that it indicates a role for the early kidney clock in the regulation of target genes that are known to contribute to the maintenance of fluid and electrolyte homeostasis.

The findings of Meszaros et al. support the intriguing concept that clock genes begin oscillating in the kidney earlier than they do in other tissues. Specifically, Rev-erba and Per2 showed rhythmic expression at E20 in the kidney whereas others have shown that the core clock genes do not exhibit significantly rhythmic expression in the liver⁷ or heart⁸ until after birth. Meszaros et al. demonstrated that α ENaC, Sgk1, NHE3 and Avpr2 all exhibited rhythmic oscillation at E20 (Meszaros et al. *Kidney International* 2014). Others have investigated rhythmic fluctuations in Per1 or Per2 promoter luciferase activity in cultured kidney extracts from transgenic rodents^{9, 10}. However, a unique aspect of the study by Meszaros and colleagues is that it is the first to investigate oscillating expression of endogenously expressed core clock genes and circadian target genes in the kidney. This work thus extends the earlier findings of others by evaluating circadian expression of endogenously expressed genes encoding proteins that are known to contribute to renal function.

Food cues are known to contribute to the timing of rhythmic gene expression in peripheral tissues¹¹. In their study, Meszaros et al. provide evidence that oscillating clock gene and target gene expression correlates with nutritional cues. For example, video monitoring of nursing pups demonstrated that young rats received most of their nutrition during the light cycle, while the mothers rested. This correlated with the timing of the acrophase, or peak, of gene expression in the neonate kidney. Of note, the circadian expression of most of the genes tested in this study underwent a phase shift corresponding to changes in the timing of food intake that occurred with weaning. Further evidence for the role of nutritional cues in the entrainment of the developing kidney clock was provided with the interesting finding

that when mothers were removed from the nursing pups during the time of maximal feeding for seven consecutive days, Bmal1 expression was inverted and the rhythmic mRNA expression of Rev-erba, Per2, Cry1, α ENaC, Sgk1, NHE3 and Avpr2 was completely lost.

Much work remains to be done to increase our understanding of how the kidney clock develops in early life. Meszaros et al. have clearly demonstrated a role for maternal nutritional cues in this process but the role of light remains to be explored. Studies in constant darkness may help determine the relative contribution of light cues versus food cues to the developing kidney clock. As noted by the authors, another way to explore this issue would be to replicate the present study using SCN-lesioned mothers. Studies in mice using global or tissue-specific clock gene knockouts may also help delineate the mechanism underlying the ontogeny of renal rhythms. A role for melatonin has been proposed in the development of the adrenal circadian clock¹² but it is unknown if this hormone acts on the kidney clock machinery.

The groundbreaking work presented here by Meszaros and colleagues convincingly establishes the existence of a kidney clock in the late fetus and early neonate. Future studies will aid our understanding of the mechanisms underlying the ontogeny of the renal circadian clock.

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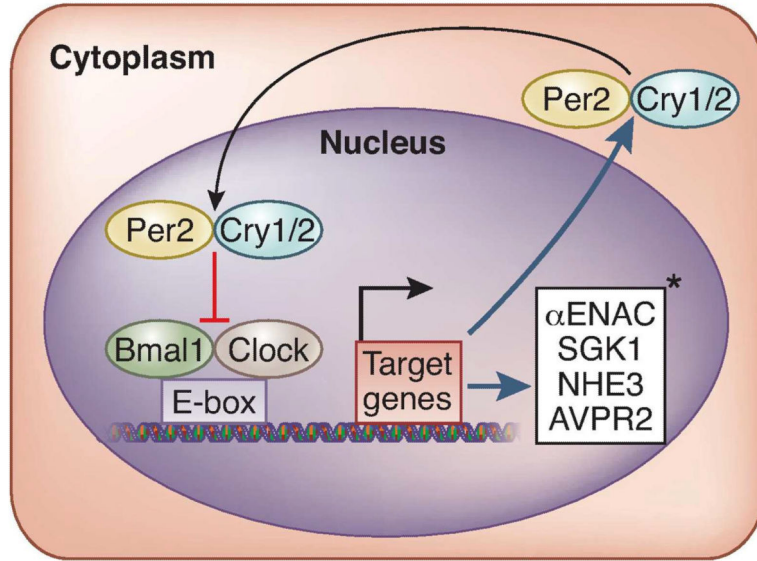


Figure 1. Transcriptional mechanism of the circadian clock

On a basic level, the circadian clock mechanism consists of a transcriptional/translational feedback mechanism. In the positive loop, the circadian rhythm proteins Bmal1 and Clock heterodimerize and interact with E-box response elements in the promoters of target genes. In the negative loop, the products of the Per2 and Cry1/2 target genes feedback on and inhibit the action of Bmal1/Clock, thereby inhibiting their own transcription. As discussed in the study by Meszaros et al. (REF) a number of kidney specific target genes, presumably regulated by the circadian clock mechanism, exhibit oscillations in mRNA expression. *The kidney-specific target genes tested in this study were αENaC (alpha subunit of the epithelial sodium channel), SGK1 (serum and glucocorticoid-regulated kinase 1), NHE3 (sodium/hydrogen exchanger), and AVPR2 (vasopressin receptor 2). Not pictured: Rev-erba, a Bmal1/Clock target gene encoding a nuclear orphan receptor which in turn mediates negative regulation of Bmal1 gene expression.