Role of Circadian Rhythms in Potassium Homeostasis

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Summary: It has been known for decades that urinary potassium excretion varies with a circadian pattern. In this review, we consider the historical evidence for this phenomenon and present an overview of recent developments in the field. Extensive evidence from the latter part of the past century clearly shows that circadian potassium excretion does not depend on endogenous aldosterone. Of note is the recent discovery that the expression of several renal potassium transporters varies with a circadian pattern that appears to be consistent with substantial clinical data regarding daily fluctuations in urinary potassium levels. We propose the circadian clock mechanism as a key regulator of renal potassium transporters, and consequently renal potassium excretion. Further investigation into the regulation mechanism of renal potassium transport by the circadian clock is warranted to increase our understanding of the clinical relevance of circadian rhythms to potassium homeostasis.

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Circadian patterns in renal electrolyte excretion in human beings have been known to exist for many years. Mills,[1] in his encyclopedic review in 1966, described sodium, potassium, water, and numerous other substances showing circadian excretion. Renal function, and a vast array of physiologic processes including sleep, physical activity, secretion of hormones, intermediate metabolism, and the metabolism and excretion of drugs, show circadian rhythms. By definition, a circadian process shows oscillation under constant conditions (ie, in the absence of a light/dark cycle). Circadian rhythms show a peak (maximum) and minimum magnitude approximately 12 hours apart, and they are driven by a circadian pacemaker in the suprachasmatic nucleus (SCN) of the hypothalamus (the central clock). The intrinsic 24-hour cycle of the clock is synchronized by the ambient light/dark cycle and also by feeding cues. The central clock, in turn, entrains pacemakers in individual cells of various organs throughout the body, termed peripheral clocks. The rhythm displays an approximate 24-hour cycle length in the absence of external entraining signals, hence the term originated by Halberg, "circa diem," meaning approximately 1 day.[1] The circadian cycle for potassium is validated by its demonstration in the absence of changes in other factors that modify potassium excretion. The magnitude of potassium excretion at a given time results from the summed effects of a number of controlling pathways, including that of the circadian rhythm.

Circadian rhythms are not unique to human beings or other mammals. Quite the contrary, they are found in a wide variety of species, from bacteria to multicellular organisms, plant as well as animal, in each case being driven by an oscillator. This review focuses on the circadian rhythm of potassium by the mammalian kidney. The rhythm is considered an important component of the complex mechanism that enables the kidney to maintain the total body potassium within a limited range despite wide variations in potassium intake. In other words, it is a component of the system responsible for potassium homeostasis.

REACTIVE AND PREDICTIVE HOMEOSTASIS

Homeostatic control of potassium excretion was attributed to a reactive system for many years, that is, a system that reacts to the magnitude of potassium intake by regulating the magnitude of excretion.[2] A negative feedback system with two kaliuretic components, the plasma concentrations of potassium and aldosterone, was considered to be a unique and sufficient mechanism for the homeostatic regulation of potassium excretion. According to this paradigm, oral intake of potassium, when absorbed, increased the plasma potassium concentration. This had a dual effect: a direct stimulation of distal tubular potassium secretion and a stimulation of the secretion of aldosterone, the adrenal steroid hormone possessing potent antinatriuretic as well as purportedly kaliuretic properties. Both plasma potassium and aldosterone acted to stimulate potassium secretion by the principal cells of the distal nephron

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and collecting duct. This active potassium secretion added significantly to the potassium potentially destined for urinary potassium excretion. Discovery of distal nephron potassium reabsorption added a second primary active transport component.[3] This reabsorption depended on a hydrogen for potassium exchange by a luminal membrane H, K-adenosine triphosphatase (ATPase) in intercalated cells and was activated during reduced potassium intake. Another reactive component was introduced with the proposal and demonstration of a splanchnic reflex control of potassium excretion.[24,5] Current views indicate this reflex is initiated in response to local changes in the potassium concentration in gut, hepatic portal vein, or liver. It is thought to act through two pathways. One pathway involves vagal nerve afferent signals to the central nervous system (CNS) that initiate efferent signals from the CNS to the kidney[4,6]; a second pathway acts through a direct stimulation of a kaliuretic "gut factor."[4,7] This reflex constitutes a feed-forward control system: signals initiating the increased excretion are not altered by the excretion itself.

Moore-Ede[8] noted that circadian cyclic excretion constituted a "predictive" homeostatic system in that it anticipated and enhanced the capacity of the nephron to perform its reactive response during the times of the 24-hour cycle when intake was greatest. Thus, peak circadian excretion of sodium and potassium in human beings occurs in the day and in nocturnal rodents at night.

Circadian rhythms of potassium and sodium have been identified in human beings, the squirrel monkey, rats, and mice.[4,9] Studies on the underlying genetic and molecular mechanisms of the circadian system in renal cells have been almost entirely performed in mice. Notably, the elegant and persuasive study of Sarelius and Greenway[10] showed the absence of circadian cyclic potassium excretion in sheep. Within the 24-hour cycle the circadian rhythm can produce wide swings in excretion. In the rat, for example, the ratio of peak to minimum excretion lies in the ranges of 4:1 to 10:1 (reviewed by Rabinowitz[4]); in human beings on a normal potassium diet, ratios on the order of 5:1 are found.[11] Thus, the ratio between the normal intraday excretion peak and the minimum may exceed changes in 24-hour excretion produced by large alterations of dietary potassium intake, making it a potent control system.

REGULATION OF THE PERIPHERAL KIDNEY CLOCK

Some mechanism of transmitting CNS clock activity to the oscillators in renal tubule cells must exist or the two would have independent oscillation patterns. Two possible pathways, neural and humoral, exist. Mills[1] noted the likelihood of a humoral pathway on the basis of circadian rhythmic excretion in a transplanted human kidney. More recently, Guo et al[12] provided direct evidence for a humoral pathway in rats using parabiosis studies, but the humoral substance or substances that carry the message is unknown and constitutes a major unsolved mystery. Recent and ongoing studies have focused primarily on the nature of the oscillator system in renal cells responsible for circadian variations in transport. It is reasonable to assume this system includes cell receptor(s) of CNS signal(s), intracellular messengers and effectors, and membrane transporters, although a coherent picture of this intracellular system has not yet emerged.

We note some of the complexities of this problem as they relate to circadian cycles of potassium and sodium. In all species studied to date in which these rhythms occur, peak excretion of potassium and sodium overlap and occur at virtually the same time in the 24-hour cycle. It is thought that the peak in sodium excretion corresponds to a reduction in sodium reabsorption and a peak in potassium corresponds to an increase in potassium secretion.

An experiment in rats to determine if the secretion of potassium by the amiloride-sensitive principal cells was responsible for the peak in potassium excretion provided strong support for this assertion.[13] Amiloride given at the time of peak potassium and sodium excretion decreased the peak excretion of potassium by 80%. Simultaneously, sodium, which is absorbed by the principal cells concurrently with potassium secretion, showed a 3.7-fold increase in excretion. At the time of minimum circadian excretion it was shown that both potassium secretion and sodium reabsorption by the amiloride-sensitive principal cells was a small fraction of the rates at the time of peak excretion. This finding localized the majority of peak potassium circadian excretion to an amiloride-sensitive mechanism consistent with the action of amiloride on the cortical collecting duct (CCD) potassium secretion, but also showed that amiloride-sensitive sodium absorption persisted during maximal natriuresis. Additional evidence for the independence of nephron sites generating the sodium and potassium cycles included an earlier onset for the potassium peak[14] and different resynchronization patterns for the urinary rhythms of sodium and potassium in rats after light-dark shifts.[15]

These results raised the question as to which cells in the nephron had decreased sodium reabsorption at the time of peak sodium excretion. They also raised a fundamental general question. If more than one cell type was involved in the generation of the cycles of different ions and of water, one had to ask whether intracellular tubular clocks were responding to different signals from the CNS oscillator, each signal directed to the control of a specific substance and a specific cell. The alternative was that there was a single