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肾脏功能稳态和损伤的生物钟调节机制

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摘要 肾脏在维持机体水电解质、酸碱平衡及代谢稳态过程中发挥重要作用, 也是调节血压的重要脏器. 生物钟在肾脏生理功能稳态维持中发挥重要作用, 肾血流量、肾小球滤过率、肾小管重吸收、激素分泌等都呈现出显著的昼夜节律变化. 除参与肾脏生理稳态调节外, 生物钟也与多种肾脏疾病存在密切联系, 生物钟紊乱会加速肾脏损伤的发生发展, 慢性肾脏病和高血压也常伴随机体生物钟紊乱. 因此, 对肾脏生物钟的研究已成为肾脏基础和临床研究中不可忽视的一部分. 本文主要介绍和总结了生物钟的分子调节机制及近年来生物钟在肾脏生理稳态维持和疾病病程进展中作用及机制的重要研究成果, 并对未来研究方向进行展望, 以期促进生物钟研究和时间生物钟学在肾脏相关学科中的应用.

关键词 生物钟, 肾脏, 水电解质稳态, 高血压, 急性肾损伤, 慢性肾脏病

肾脏的基本功能是生成尿液, 借以清除体内多余的代谢产物及毒性物质, 同时经重吸收功能保留水分及葡萄糖、蛋白质、氨基酸、钠离子、钾离子等有用物质, 以调节水电解质及酸碱平衡[1]. 肾脏同时还有内分泌功能, 可通过分泌肾素、促红细胞生成素、活性维生素D3、前列腺素等, 保证机体血压和内环境的稳定[2]. 根据2019年全球调查数据显示, 目前全世界至少有8.5亿人患有肾脏疾病, 其中中国的患病人数高达1.3亿, 预计2040年, 慢性肾脏病(chronic kidney disease, CKD)将成为危害人体生命健康的第五大最常见原因[3].

生物钟, 顾名思义, 生物体内的计时装置, 是机体为了适应外界环境变化进化而来的一种内在稳态调控系统, 其主要作用是对外部环境变化做出恰当的周期性的反应, 从而保持内环境稳态. 哺乳动物的多种行为和生理活动, 如睡眠觉醒、体温调节、血压改变、激素合成及细胞因子释放等, 都表现出以24 h为周期的昼夜节律(也被称为近日节律)[4]. 生物节律还有年节律、季节律、月节律等, 但因昼夜节律相对更密切地参与和影响人类的活动与健康而备受关注, 所以本文探讨的生物钟主要是指产生和调节昼夜节律的内在生物钟. 生物钟由位于下丘脑视交叉上核(suprachiasmatic nucleus, SCN)的中央时钟和外周组织的外周时钟构成(图1(a)). 中央时钟是控制哺乳动物产生昼夜节律的主振荡器, SCN接收来自视网膜的光信号, 将其转化为各种神经体液信号, 传递到其他外周组织, 进而协同调节机体各种生理活动的昼夜节律[5]. 除中央时钟外, 每个外周器官或细胞都有自己的内部时钟即外周时钟. 研究表明, 位于各组织器官的外周时钟也能独立于中央时钟而发挥作用, 如SCN损伤的小鼠, 外周器官仍表现出恒定的节律性[6]; 离体的小鼠心脏、肾脏等也均具有时钟基因的节律性表达[7,8]. 外周生物钟主要受激素、食物、温度和代谢产物等的调控[9]. Zhang等人[10]利用转录组学分析小鼠12 个组织器官的基因表达情况, 发

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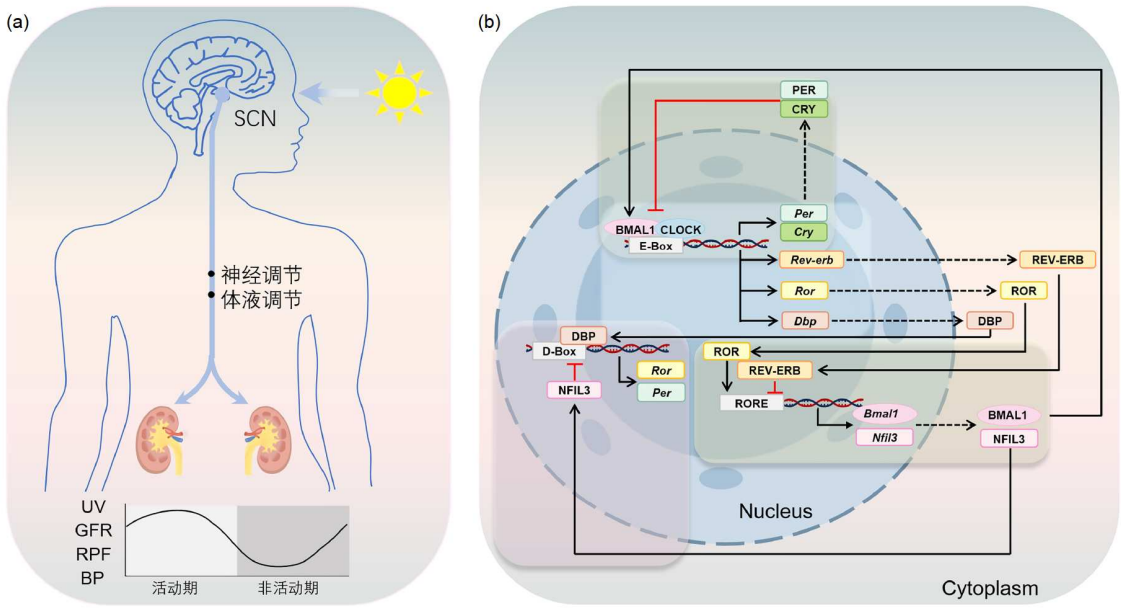

图 1 生物钟调控的分子机制. (a) 当光线通过视网膜刺激感光细胞, 使其信号传至SCN, 通过神经和体液信号传至外周生物钟如肾脏, 从而实现中枢与外周生物钟同步化. 肾脏的很多生理功能如尿量(UV)、肾小球滤过率(GFR)、肾血流量(RPF)、血压(BP)等都具有显著昼夜节律. (b) BMAL1和CLOCK形成的异二聚体位于激活回路, 激活下游靶基因. PER和CRY异二聚体位于抑制回路, 抑制BMAL1/CLOCK异二聚体及其自身的表达. REV-ERB、NFIL3分别与ROR、DBP竞争结合RORE、D-Box元件, 转录抑制下游靶基因

Figure 1 Molecular mechanisms of circadian clock regulation. (a) Light activates the photoreceptor cells in the retina, and the resulting signal is transmitted to the central clock suprachiasmatic nucleus (SCN). Then the SCN synchronizes with peripheral clocks, such as the kidney through neural and humoral signaling. Many renal physiological functions, including urine volume (UV), glomerular filtration rate (GFR), renal blood flow (RPF), and blood pressure (BP), exhibit significant circadian rhythms. (b) Several transcription-translation feedback loops are involved in the molecular mechanisms of the circadian clock. The BMAL1 and CLOCK proteins function as activators, promoting the expression of downstream target genes. In contrast, the PER and CRY proteins act as repressors, inhibiting the expression of both BMAL1/CLOCK and their own genes. REV-ERB and NFIL3, through competitive binding to RORE and D-Box elements respectively, along with ROR and DBP, repress the transcription of downstream target genes

现在所有编码蛋白质的基因中, 有43%的基因在转录水平呈现昼夜节律, 且大部分表现为器官独有的节律特征. 其中, 肾脏是仅次于肝脏的表达节律基因最为丰富的外周组织器官. 以狒狒为研究对象, 研究证明灵长类动物的肾脏组织也有着丰富的节律基因表达[11,12].

生物钟对机体健康的重要性在过去几十年的流行病学研究中已得到充分证明. 研究表明, 生物钟紊乱会导致多种不良健康后果, 如睡眠-觉醒障碍、神经和精神疾病、心血管疾病、癌症、自身免疫性疾病等[13]. 越来越多的证据表明, 生物钟紊乱在肾脏疾病的发生发展中也起着重要作用. 比如, 夜间轮值班的人群CKD和高血压的患病率均明显增加[14,15]. CKD患者也通常伴随睡眠、血压和蛋白尿的昼夜节律紊乱[16]. 此外, 白天行肾移植手术的病人预后要优于晚上手术组[17]. 因此, 生物钟紊乱和肾脏损伤密切相关, 阐明生物钟在肾脏生理稳态和病理损伤中的作用和机制, 对急慢性肾损伤及其并发症的防治具有重大意义.

1 生物钟的分子机制

在分子水平, 哺乳动物的生物钟是由一系列核心生物钟基因和钟控基因组成的转录-翻译反馈回路(transcription-translation feedback loop, TTFL)共同调节的结果[18]. 2017年诺贝尔生理学和医学奖授予了发现调控生物钟分子机制的3位美国科学家. 首先, BMAL1 (brain and muscle arnt-like 1)和CLOCK(circadian locomotor output cycles kaput)或CLOCK类似物NPAS2(neuronal PAS domain protein 2)形成异二聚体, 激活启动子和/或增强子区域中含有E-box元件的靶基因的转录, 如PER(period)和CRY(cryptochrome)蛋白家族的成员, 形成正反馈. 当PER和CRY蛋白积累到一定程度后, 进入细胞核, 反向抑制BMAL1-CLOCK的转录, 进而抑制自身的表达, 此时BMAL1- CLOCK的新转录周期再次启动, 形成负反馈. BMAL1-CLOCK也可以激活核受体REV-ERB(nuclear receptor subfamily 1, group D member)的基因转录, 使其与核受体ROR(RAR-related

orphan receptor)竞争结合*Bmal1*启动子区RORE反应元件, 使其反向振荡, 形成第二个TTFL环. 此外, BMAL1-CLOCK还可以激活DBP(D-box binding protein), DBP与NFIL3(nuclear factor interleukin 3)构成另一个稳定反馈回路, 通过与*Per*和*Ror*启动子区D-box反应元件相结合并对其转录进行调控[19]. 上述3个TTFL共同构成了复杂的生物钟调控核心机制, 调控众多下游基因即钟控基因(clock controlled genes, CCG)的节律性表达[20](图1(b)). 受这一保守生物钟分子机制的调控, 大量与肾脏功能相关的基因均呈现出昼夜节律的表达模式, 如水通道蛋白2(aquaporin2, AQP2)、血管加压素受体2(vasopressin type 2 receptor, V2R)、钠-氢交换体(Na^+/H^+ exchanger 3, NHE3)、钠氯协同转运蛋白(Na^+/Cl^- cotransporter, NCC)、上皮钠离子通道(epithelial Na^+ channel, ENaC)、有机溶质转运体家族成员(solute carrier family 6 member 9, SLC6A9、solute carrier family 6 member 6, SLC6A6), 以及参与维持足细胞功能的蛋白(transcription factor 21, TCF21、cathepsin L, CTSL)等相关基因在肾脏中均呈现出昼夜节律表达模式[21], 最终共同调控肾脏多种细胞和生理功能的昼夜振荡.

2 生物钟与肾脏水稳态调节

正常人体一天需要补充约3 L左右的水分, 其中仅有1%的水通过呼吸、出汗、排便、排尿等生理行为排出体外, 99%的水被肾脏重吸收回到血液循环, 所以肾脏是调节机体水稳态最重要的组织脏器. 肾脏的功能单位是肾单位, 包括肾小体和肾小管两部分. 肾小体包括肾小球和肾小囊, 其中肾小球是一团毛细血管网, 充当过滤大量血液的过滤屏障, 人体每天经肾小球过滤的血液高达180 L. 肾小管主要包括近端小管、髓袢、远端小管和集合管, 其中肾脏对水的重吸收主要包括由近端小管水通道蛋白1(aquaporin 1, AQP1)介导的组成性重吸收和由集合管(aquaporin 2-4, AQP2-4)、抗利尿激素(antidiuretic hormone, ADH)共同介导的可调节性重吸收而实现, 经过肾小管重吸收, 人体每天产生的终尿仅为1.5 L左右[22].

研究表明, 肾脏参与水稳态调节的很多生理过程都表现出昼夜节律特征. 比如, 哺乳动物的肾血流量、肾小球滤过率、尿量都等均表现出明显的昼夜节律变化, 主要表现为活动期增加, 非活动期减少. 影响肾小球滤过率的因素包括血压、入球出球小动脉的阻力、交感神经活动、肾素及血管紧张素的分泌也都有着明显的昼夜节律[16]. 众所周知, 肾脏功能与饮水摄食行为密切相关, 而正常情况下机体的饮水和摄食行为均具有显著的昼夜节律, 因此在一定程度上会对肾脏内在生物钟的研究产生干扰. 1977年美国生理学杂志发表的一项研究表明禁水禁食并不能使尿量产生的昼夜节律振幅降低或消失[23], 同时我国科学家的一项最新研究也表明昼夜颠倒的摄食行为也不会对肾脏节律基因的表达谱产生很大影响[24,25]. 因此肾脏的水稳态调节可独立于摄入行为之外受内在生物钟调控. 正常情况下, 排尿的峰值主要发生在早晨, 而晚上可以几乎不发生, 这与夜间血浆ADP又称精氨酸加压素(arginine vasopressin, AVP)的升高以及肾小球滤过率的降低有直接关系[26]. 2013发表的一项临床数据结果也显示, 7~15岁健康儿童的血浆AVP存在明显的昼夜节律变化, 主要表现为夜间升高, 并且这一变化不受性别和青春期的影响[27]. 此外, AQP2在尿液中的排泄量会随着AVP的增加而增加[28], 且健康成年人尿液中AQP2与ADH的排泄均表现出上午下降, 下午和晚上升高的趋势, 这与夜间尿量减少的生理现象一致[29](图2). 利用核心生物钟基因敲除小鼠进行研究发现, *Clock*$^{-/-}$小鼠可呈现尿崩症表型, 表现为饮水量和尿量显著增加, 这可能与其AQP2和V2R的肾脏表达显著降低有关[21]. 同样, 我们的研究发现, 与*Clock*$^{-/-}$小鼠一致, 出生后敲除*Bmal1*基因的小鼠夜间尿量显著增加且尿量排泄昼夜节律明显消失[30]. 值得一提的是, 我们和他人的研究均没有发现肾小管特异性*Bmal1*敲除小鼠的尿量及其昼夜振荡谱与对照组有显著差异[31], 但足细胞*Bmal1*特异性敲除小鼠的肾小球滤过率的节律发生了明显变化, 由原来的昼夜节律变为超日节律[32], 提示足细胞内在生物钟对肾小球滤过率的昼夜节律维持更为重要. 同样, *Per1/2*双敲除小鼠虽在明-暗循环中的尿量变化仍存在昼夜节律, 但暗-暗循环条件下则完全失去昼夜节律变化, 且总体尿量显著高于对照小鼠[26]. 有研究表明, 部分参与水电解质稳态调节的重要基因受到核心生物钟基因的转录调控, 比如钠-氢交换体*Nhe3* 是BMAL1/CLOCK 的直接靶基因, BMAL1/CLOCK通过结合*Nhe3*启动子区的E-box 调节其节律性表达[33]. 在129/sv小鼠的研究中, PER1的药理学阻断剂PF670462会使*Nhe3*和钠-葡萄糖共转运蛋白1(sodium glucose cotransporter 1, SGLT1)的mRNA表达降低, 而钠-葡萄糖共转运蛋白2(sodium glucose cotransporter 2, SGLT2)保持不变[34]. 综上, 核心生物钟基因在肾脏水稳态调节中

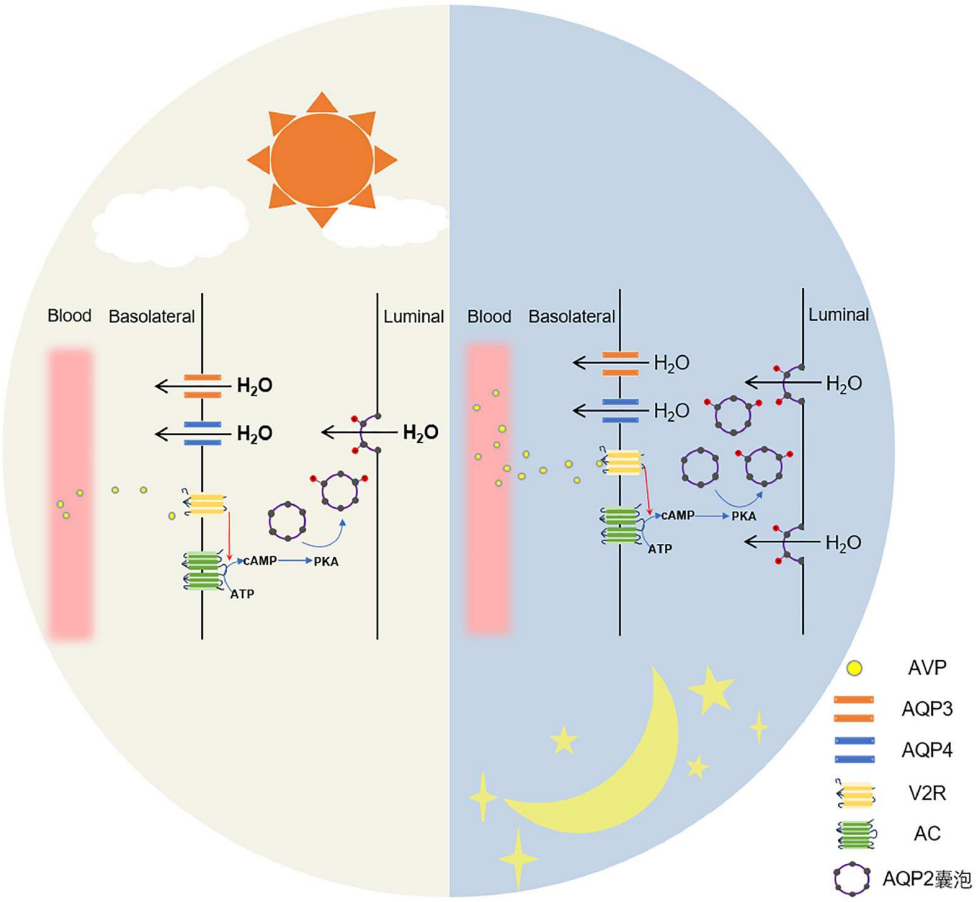

图 2 肾脏集合管水重吸收的昼夜节律变化. 以人类为例, 相较于白天, 夜间循环中的AVP含量增加, 通过受体V2R进入主细胞, 刺激AQP2由囊泡转移至质膜, 从而增加肾小管腔内水的重吸收. 这一生理现象导致夜间水重吸收增加, 尿量减少

Figure 2 Circadian rhythms of water reabsorption in the renal collecting duct. In humans, the circulating level of AVP is higher at night than during the day. This increase in AVP stimulates water reabsorption by promoting the transport of AQP2 from vesicles to the apical plasma membrane through the V2R receptor in the principal cells of the collecting duct. As a result, water reabsorption is enhanced during the night, leading to a decrease in urine volume

发挥重要作用, 但其主要发挥作用的主要部位和具体分子机制尚需要进一步明确.

3 生物钟与肾脏电解质稳态调节

尿液中的电解质主要包括钠离子、钾离子、氯离子、钙离子和磷酸盐. 科学家发现, 不论是人类还是大鼠, 尿电解质的排泄都具有明显的昼夜节律变化[35,36]. 在健康个体, 活动期的尿电解质排泄较静息期总体增多, 但钠、钾和氯化物排泄的昼夜节律变化并不完全一致[37]. 以人类为例, 尿钠和肌酐排泄的昼夜节律在一定程度上表现出同步性, 夜间达到峰值, 早晨有所下降, 中午和下午达到最低值[38]. 肾上腺分泌的盐皮质激素醛固酮是调节尿电解质稳态的一个重要激素, 其主要作用于肾脏远曲小管和集合管上皮细胞, 增加钠离子水的重吸收而促进钾离子的排泄. 研究表明, 血液中的醛固酮水平存在显著昼夜节律, 主要表现为睡眠期间增加, 是造成尿钠尿钾排泄产生昼夜节律的重要原因之一[39]. 生物钟对醛固酮的合成和释放至关重要, 核心生物钟基因*Clock*缺失可导致醛固酮分泌的昼夜节律完全消失[40], 而*Cry1*/*2*可通过影响醛固酮合成限速酶(hydroxy-delta-5-steroid dehydrogenase, 3 beta- and steroid delta-isomerase 6, HSD3B6)的节律表达进而影响血浆醛固酮的释放, 参与尿电解质稳态调控[41], 钟控基因*Dbp*、*Hlf*和*Tef*的三敲小鼠也表现出较低的血浆醛固酮水平[42]. 除影响醛固酮水平外, 生物钟基因也可通过直接调控钠转运相关蛋白的表达(图3), 除上述提到钠-氢交换体*Nhe3*受转录调控外, 肾脏上皮细胞钠通道(*Enac*)的转录表达也受PER1和CLOCK蛋白的转录调

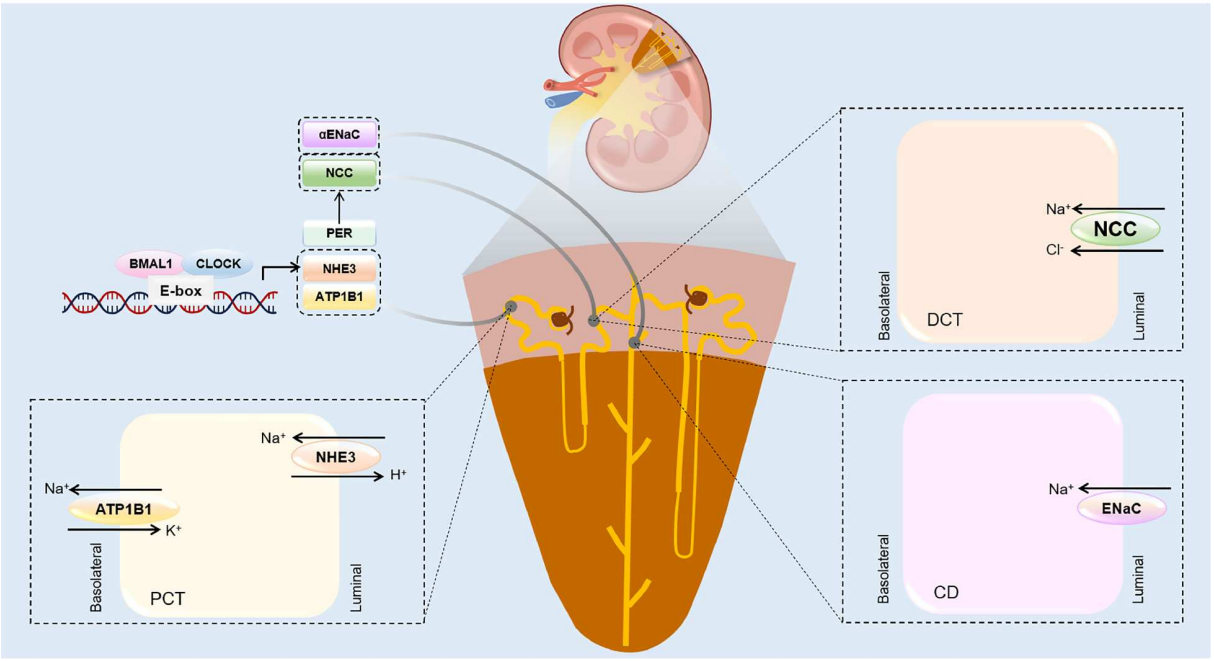

图 3 生物钟对肾脏钠离子转运相关基因的转录调控机制. BMAL1、CLOCK和PER可通过在近端小管转录调控*Nhe3*、*Atp1b1*, 在远端小管转录调控*Ncc*、及在集合管转录调控*αEnac*等基因的节律表达, 共同调控钠离子稳态

Figure 3 Circadian Regulation of Transcription of Sodium Ion Transport-Related Genes in the Kidney. BMAL1, CLOCK, and PER regulate the transcription of sodium transport-related genes in a circadian manner. In the proximal tubules, they control the rhythmic expression of *Nhe3* and *Atp1b1*. In the distal tubules, they regulate the transcription of *Ncc*, while in the collecting ducts, they control the expression of *αENaC*. Together, these mechanisms coordinate sodium ion homeostasis in the kidney

控, *Per1*基因敲除小鼠*Enac*表达水平明显下降, 尿钠排泄增加[43]. 此外, *Ncc*、*Nkcc2*、*Sglt1*等也可能受*Bmal1*、*Clock*、*Cry*和*Per*等核心时钟基因的昼夜节律调节[44]. 与尿钠昼夜节律略有不同, 尿钾排泄主要在清晨达到峰值, 之后开始下降, 直到傍晚达到最低水平[38]. 钾离子排泄受血浆醛固酮水平和肾脏远端小管对钾离子转运和排泄的共同调节, 但目前关于尿钾排泄的昼夜节律与醛固酮的关系尚有争议. 在一项CKD患者的研究中发现, 尿钾排泄的昼夜节律主要受尿钠水平影响, 这可能与醛固酮保钠排钾的生理功能相关[45]. 但另一项研究中, 在给健康成年男性使用利尿剂呋塞米抑制NKCC2, 发现尽管尿钠分泌和醛固酮的水平都受到显著影响, 但尿钾排泄尤其是夜间显著下降的昼夜节律现象不受影响, 提示钾离子排泄的昼夜节律控制也可能与尿钠水平和醛固酮无关[46]. 关于尿钾排泄昼夜节律的明确机制及核心生物钟分子在其中的作用尚需要进一步研究. 此外, 有研究报道*Dec1*可以跟CLOCK/BMAL1竞争结合E-box参与Na^+/K^+-ATP酶β1亚基*Atp1b1*的启动子活性调控, 进而调控钠钾分泌和血压昼夜节律的稳态[47]. 在健康人体中, 尿液中氯化物、钙离子和磷酸盐的水平也具有明显的昼夜节律变化特征, 氯化物、尿钙的昼夜节律主要表现为下午到夜间达高峰, 凌晨到早晨达低谷, 而尿磷酸盐排泄的昼夜节律主要表现为上午最低, 随后持续升高, 凌晨略有下降, 但其昼夜节律调控机制均尚未明确[48~50].

4 生物钟与肾脏血压调节

肾脏是维持机体血压稳态的最重要器官之一, 主要通过调节机体水电解质平衡及分泌激素(如肾素)等影响血压变化, 而正常的血压对于维持肾脏的正常血供至关重要, 因此二者相互影响, 互为因果. 血压的昼夜节律是人们最为熟知的昼夜节律现象之一, 正常成年人的动脉血压在夜间维持较低水平, 清晨迅速升高, 早上8~10点达到高峰, 随后下降, 但仍维持在较高水平(部分人群下午最高), 夜晚入睡后, 血压持续下降至最低[51]. 一般来讲, 健康人夜间血压会比白天血压下降10%~20%, 称为杓型血压. 夜间血压不下降或下降低于10% 均被称为非杓型高血压, 部分患者甚至还会出现夜间较白天血压更高. 血压的昼夜节律改变是高血压患者发生心脑血管并发症的主要原因之一[52,53]. 在

健康人群和高血压患者的几项大型前瞻性研究发现, 血压是肾脏损伤的独立危险因素, 血压越高, 终末期肾病(end-stage kidney disease, ESKD)的发病风险越大[54]. 多数慢性肾脏病(CKD)患者的动态血压显著升高主要发生在夜间睡眠时, 而非CKD患者的动态血压一般表现为白天升高明显, 因此CKD患者出现非杓型高血压的比例要显著高于非CKD患者. 睡眠期平均收缩压升高是诊断CKD患者高血压和治疗性血压控制不佳的主要依据[55].

4.1 核心生物钟基因与血压昼夜节律

临床GWASs大数据分析提示生物钟基因*Bmal1*的单核苷酸多态性突变可能与原发性高血压的发生存在相关性[56]. 我们通过对出生后*Bmal1* 基因敲除小鼠的研究发现, 基础血压的昼夜节律振荡主要受控于生物钟, 且在非正常光照环境下不随行为的节律变化而变化[57]. 因此, 不论是出生前还是出生后全身敲除小鼠的*Bmal1*基因均可导致血压昼夜节律的完全消失[58,59]. 有趣的是, Johnston等人[60]发现*Bmal1*基因全身缺失大鼠的血压昼夜节律依然存在. 因此, 生物钟在血压昼夜节律调控中的作用可能存在种属差异. 摄食行为改变对血压昼夜节律的影响也有报道, 持续一周的白天限制性摄食被报道可通过改变肾脏节律蛋白振荡或调节交感神经通路改变等完全逆转小鼠血压的昼夜节律[61], 但对尿钠尿量的昼夜节律没有影响[59]. 与*Bmal1*一样, 其他几个核心生物钟基因如*Clock*、*Per1*/*2*、*Cry1*/*2*的基因突变或敲除也会不同程度改变血压水平的昼夜节律[21,41,62,63].

4.2 生物钟参与血压调节的机制

关于生物钟在血压稳态调节中的作用机制也有很多报道. 比如, 生物钟可能会参与对肾素-血管紧张素-醛固酮(renin-angiotensin-aldosterone system, RAAS)系统的作用调节[64], 而RAAS系统的节律改变会显著影响高血压及其相关并发症的发生[65]. 核心生物钟基因*Cry1*和*Cry2*双敲除小鼠的血浆醛固酮分泌显著增加, 因此更容易发生盐敏感性高血压[41]. *Clock*、*Per1*也可能通过影响醛固酮受体及其下游靶基因的转录表达进而参与高血压的发生发展[66]. 血管外周脂肪组织*Bmal1*通过调节血管紧张素原的表达, 进而影响血管紧张素II (angiotensin II, AngII)的水平, 调节血压[67]. 除RAAS系统外, 生物钟也可影响内皮素1(endothelin-1, ET1)、一氧化氮(nitric oxide, NO)、20-羟-二十烷四烯酸(20-hydroxyeicosatetraenoic acid, 20-HETE)等与血压密切相关的激素的分泌[68]. 研究表明, *Per1*基因敲除可能通过减少收缩血管的活性物质ET1的水平而降低雄性129/sv小鼠(但非C57BL/6小鼠)的动脉血压[62,69], 且*Per1*对ET1的调节可能存在性别差异[70]. *Clock*基因可能通过直接或间接影响肾脏20-HETE的分泌参与对血压稳态的调控[40]. 肾素是由肾脏的交感神经刺激分泌, 对血压的升高起着关键作用. 研究表明, 瞬时受体电位阳离子通道亚家族M 成员6(transient receptor potential melastatin 6, TRPM6)是一个Mg^{2+}渗透性阳离子通道, 在活动期增强肾素分泌中发挥作用, 肾脏特异性*Trpm6*缺陷小鼠的血压降低, 且血压的昼夜变化完全消失, 提示TRPM6在血压调节中起着至关重要的作用, 特别是在维持血压昼夜节律性变化方面, 但关于TRPM6是否受生物钟直接调控尚不明确[71]. 血清钠离子稳态跟血压水平和节律也密切相关, 慢性CKD和高血压患者, 血压改变通常伴随尿钠排泄的昼夜节律改变, 因此上部分提到的生物钟参与钠离子稳态调控的机制也是血压稳态调控的重要组分.

4.3 肾脏局部生物钟与血压节律稳态

研究表明, 包括肾脏在内的外周生物钟是机体维持血压昼夜节律稳态的重要组成部分. 肾脏核心生物钟基因*Bmal1*、*Clock*、*Per2*等的表达和节律在遗传性高血压大鼠或其他高血压动物模型中均会发生明显改变[72~74]. 研究表明, 分泌肾素的颗粒细胞敲除*Bmal1*会导致小鼠轻度多尿、尿钠排泄昼夜节律模式改变、血浆醛固酮水平显著降低和低血压[75]. 肾脏集合管*Bmal1*敲除降低了雄性小鼠的平均动脉压, 但对雌性小鼠没有显著影响. 同时该小鼠平均动脉压的降低主要表现为较低的舒张压, 而收缩压仅显示出趋势性的差异[76]. 远端集合管*Bmal1*敲除小鼠表现出较低的基础血压, 并且这种血压调节的重要组成部分可能是由于醛固酮敏感的远端肾单位和集合管中的Na^+转运[77]. 总之, 无论是在分泌肾素的颗粒细胞, 还是在远端小管、集合管中特异性敲除*Bmal1*基因均可观察到小鼠血压水平的下降. 值得注意的是, 目前的研究仅初步探索了*Bmal1*在肾脏各类细胞的特异表达与血压的关系, 考虑到*Bmal1*也存在其他非节律相关的功能[78], 另个别研究认为血压昼夜节律变化可能跟*Bmal1*无关[60], 其他核心生物钟基因在肾脏的局部表达及其血压昼夜稳态调控中

是否发挥优先作用也值得进一步思考. 此外, 尽管越来越多的研究提示外周生物钟在血压稳态调控中均发挥重要作用, 但各外周生物钟之间的关系以及外周生物钟与中枢生物钟的作用关系仍是血压节律调控未来研究的一个重要方向.

5 生物钟与急性肾损伤

急性肾损伤(acute kidney disease, AKI)是指由于多种病因引起的肾脏功能快速下降而出现的临床综合征, 感染、缺血、手术损伤、抗癌药物等是引起AKI发生的常见原因[79]. AKI如若治疗不及时可最终发展成CKD, 临床数据显示, AKI患者发生CKD的风险是无AKI患者的3倍以上[80]. 目前关于生物钟与AKI的关系研究相对较少. Montaigne等人在2006年至2017年研究了10291名患者肾移植后的生存率发现, 白天行肾移植手术的病人及移植物的生存率要明显优于晚上手术组, 且急性排斥反应和慢性同种异体移植肾病均在夜间较高, 提示肾脏耐受缺血的能力及免疫反应可能具有昼夜节律差异[17]. AKI的病理特征主要为肾小管上皮细胞的致死性损伤. 研究表明, *Bmal1*作为最为重要的核心生物钟基因, 可能通过维持肾小管上皮细胞的线粒体稳态或抑制核呼吸因子2(nuclearrespiratoty factor 2, *Nrf2*)介导的细胞氧化应激而延缓缺血再灌注损伤诱导的AKI进展[81,82], 也可能会通过促进细胞凋亡加速抗癌药物顺铂诱导的急性AKI发生[83]. 生物钟核受体*Rev-erbα*在AKI发生发展中也可能发挥一定的保护作用, 利用*Rev-erbα*肾脏特异性敲除以及选择性拮抗剂等的研究表明, 激活生物钟核受体*Rev-erbα*可降低小鼠对马兜铃酸诱导的铁死亡和肾损伤的敏感性[84]; 抑制*Rev-erbα/β*可改善叶酸诱导的小鼠AKI, 其机制也跟改善小管上皮细胞铁死亡的发生有关[85]. 虽然生物钟在AKI中的作用及机制研究还刚刚起步, 但越来越多的研究结果都提示生物钟与急性器官损伤的预后密切相关, 如发表在*Lancet*上的一项主动脉瓣置换术后随访的临床研究表明, 下午手术组引起的主要不良心脏事件发生率明显低于上午手术组[86]; 不同时间点行肝脏缺血再灌注损伤手术预后也存在较大差异[87], 因此深入阐明生物钟及时间生物钟学在AKI发生发展中的作用有望为防治AKI向CKD进展提供全新视角.

6 生物钟与慢性肾脏病

慢性肾脏病(CKD)是指肾脏结构与功能的慢性进展性损伤, 病程一般大于3个月, 临床主要表现为不同程度的蛋白尿、高血压、水肿、肾功能损伤, 目前较为公认的CKD病因有高血压、糖尿病、年龄相关的肾功能下降等[88~90]. 生物钟紊乱与CKD密切相关.

6.1 生物钟与CKD临床研究

临床研究表明, 夜间轮值班或相关特殊工作群体CKD和高血压的患病率均明显增加[14,15]. 慢性肾病或终末期肾病患者也通常伴随生物钟系统的紊乱, 表现为睡眠活动障碍[91] 或容易出现睡眠呼吸暂停、白天嗜睡等病理性表现[92]. 部分肾病综合征患者会出现夜间尿液浓缩能力下降以及蛋白尿排泄的昼夜节律异常[16], 并且有研究发现蛋白尿的增加与睡眠碎片化有关, 即每增加10% 蛋白尿, 约增加28%的碎片化睡眠[93]. 此外, 由于机体钠排泄能力的不足, CKD患者更易出现夜间血压升高而表现出非杓型高血压, 并由此增加中风和终末器官损伤的风险. 部分糖尿病患者会出现血压昼夜节律的紊乱的现象, 并且该现象通常早于微量白蛋白尿或其他肾脏损伤指标的出现, 提示生物节律紊乱可能是糖尿病出现肾脏并发症的重要诱因之一[94]. 综上, 生物钟紊乱和CKD有一定的双向相关性, 昼夜节律紊乱可加重CKD进展, CKD又可以进一步促进机体生物钟紊乱.

6.2 生物钟参与CKD的机制研究

与临床观察一致, 动物实验机制研究表明, 肾大部切除的CKD大鼠和腺嘌呤诱导的CKD小鼠均显示睡眠和活动度的昼夜节律异常, 且中央时钟和外周时钟均呈现异常变化[95,96]. 我们最近发表的研究证实, 长时间将小鼠暴露于昼夜颠倒的环境可显著加速肾大部切除术或梗阻性肾病的发生发展, 其机制可能与促进损伤肾脏发生炎症反应和抑制肾脏能量代谢有关[97]. 非正常灯光干扰环境同样会促进高血压大鼠肾脏损伤标志物肾损伤分子1(kidney injury molecule 1, KIM1)的分泌明显增加[98]. 肾脏纤维化是多种CKD进展至终末期肾病的共同病理特征. 通过利用肾脏组织特异性核心生物钟基因敲除小鼠[95,99]进行研究, 我们发现肾, 小管特异性缺失*Bmal1*会通过抑制肾脏谷胱甘肽代谢加重腺嘌呤饮食诱导的慢性肾损伤和肾脏纤维化[31], 但出生后全身敲除*Bmal1*基因则可通过抑制Hedgehog通路保护单侧输尿管梗阻(unilateral ureteral obstruction, UUO)诱导的肾小管间质纤维化[30]. 同样, *Clock*缺失或突变

小鼠在腺嘌呤诱导的CKD模型中表现出更为严重的肾脏损伤[95,99]，但在脱氧皮质酮和高盐饮食诱导引起肾脏纤维化模型中, *Clock* 基因突变则会部分改善肾脏纤维化[100]. 不同疾病模型、实验范式或模式动物的背景差异都可能是引起上述差异的原因，但这也提示核心生物钟分子在肾脏纤维化中发挥作用机制复杂.

6.3 生物钟与肾脏代谢紊乱

CKD的发生与肾脏内分泌和代谢功能失调存在必然联系. 研究发现，肾小管特异性细胞敲除*Bmal1*会改变血浆和肾脏的代谢功能，降低肾脏分泌阴离子药物的能力，进而影响肾脏入血物质分泌的稳态[101]. 在足细胞或肾小管中敲除*Bmal1*可通过增强肾脏近端小管

表 1 核心生物钟基因修饰小鼠的肾脏损伤表型

基因	表型	机制	文献
Bmal1	全身敲除 (traditional global KO)	GFR↓ 血肌酐↑ 血尿素氮↑ 腺嘌呤CKD↑	转录组分析, *Bmal1* KO小鼠的细胞周期、炎症和脂肪酸代谢途径相关基因明显改变.	[106]
	全身敲除 (tamoxifen-induced postanal KO)	尿量↑, 节律消失 血压↓, 节律消失 UUO纤维化↓	BMAL1通过E-box转录激活促纤维化基因*Gli2*的转录, 进而促进肾脏纤维化.	[30]
	肾单位 特异性过表达 (adenovirus administration)	血肌酐↑ 血尿素氮↑	BMAL1通过E-box转录激活肾肝化相关基因(如*Alb*、*Hp*和*Tf*)的表达.	[83]
	全段肾小管特异性敲除 (*Bmal1*$^{lox/lox}$/Pax8-rtTA/LC1)	尿量– 尿钠– 尿钾– 血压下降 STZ诱导血糖增高	转录组、代谢组明显改变, STZ诱导后肾脏糖异生途径增强.	[101,102]
	足细胞特异性敲除 (*Bmal1*$^{lox/lox}$/Nphs2-rtTA/LC1 mice)	尿量变为超日节律 尿肌酐↑	BMAL1通过调控与足细胞功能相关基因的表达(*Tcf21*、*Nsf*、*Gna12*、*Arhgap24*、*Ctsl*、*Gprc5a*等)影响肾小球滤过.	[32]
	肾素表达细胞特异性敲除 (*Bmal1*$^{lox/lox}$/Ren1-Cre mice)	尿量↑ 尿钠– 尿钾– GFR ↑ 尿肌酐 – 血压↓	参与水钠平衡的关键基因(如*Aqp2*、*Aqp4*、*αEnac* 和*Sgk1*)的表达水平呈昼夜节律时间点依赖性降低.	[75]
	近端小管 特异性敲除 (*Bmal1*$^{lox/lox}$/Kap-Cre mice)	尿量– 尿钠– 尿钾– 腺嘌呤CKD↑	BMAL1通过E-box转录激活半胱氨酸β-合成酶(CBS), 从而改善CKD小鼠的肾脏代谢, 抑制炎症纤维化.	[31]
	远端小管和/或集合管 特异性敲除 (*Bmal1*$^{lox/lox}$/ Ksp-Cre mice/ *Bmal1*$^{lox/lox}$/ Aqp2-Cre mice)	尿量– 血压下降 节律不变(雄鼠) 血压不变(雄鼠)	雌、雄小鼠对钠离子稳态的调控作用及内皮素受体ET1R表达不同.	[76,77]
Clock	*Clock*$^{\Delta19/\Delta19}$ 突变	尿量↑ 尿钠↑ 尿钾↑ 血压↑ 腺嘌呤CKD↑ DOC/盐CKD↓	CLOCK: BMAL1 通过E-box转录激活*Atp1b1*, 突变小鼠的*Atp1b1*表达降低, 血压升高, 钠钾稳态失衡. 腺嘌呤饮食后, 明胶酶(基质金属蛋白酶2和9)和腺嘌呤代谢产物在肾脏中的沉积增多, 促进肾脏损伤.	[95,99,100]
	*Clock*敲除 (traditional global KO)	尿量↑ 血肌酐ZT12↑ 尿肌酐↓ 血压↓	参与水钠平衡的关键基因(*V2r*, *Aqp-2*, *Aqp-4*, *αEnac*)的肾脏表达的显著变化.	[21]
Rev-erbα	远端肾小管 特异性敲除 (*Rev-erbα*$^{lox/lox}$/Cdh16-Cre mice)	马兜磷酸AKI↓	*Rev-erbα*降低小鼠对AAI 诱导的铁死亡敏感性.	[84]
Rev-erb-α/*Rev-er-β*	双基因全身敲除 (traditional global KO)	叶酸诱导的AKI↓	*Rev-erb-α*/*β*通过直接结合RORE顺式元件来抑制*Slc7a11*和*Ho1*(两个抑制铁死亡的基因)的转录, 从而导致AKI后的铁死亡增加.	[85]

的糖异生过程加重链脲佐菌素诱导的糖尿病[102]. 我们自己的研究发现, 调节代谢稳态的小分子化合物β-烟酰胺单核苷酸(β-nicotinamide mononucleotide, NMN)可显著改善生物钟紊乱相关的肾脏损伤[97]. 随着代谢相关肾脏疾病(如糖尿病肾病)的日益增多, 越来越多的研究提示CKD与肾脏细胞能量代谢变化, 如糖脂代谢稳态失衡密切相关, 因此进一步探索生物钟分子在肾脏代谢平衡调节中的作用可望为延缓CKD进程提供新思路.

7 生物钟与肾脏肿瘤

越来越多的证据表明昼夜节律紊乱与泌尿生殖系统癌症(包括前列腺癌、膀胱癌和肾癌)的患病率和死亡率增加之间存在联系[103]. 透明细胞癌是肾癌最常见的亚型, 约70%的肾癌为透明细胞癌. 有研究报道称肾透明细胞癌组织中CLOCK、CRY1和CRY2的表达下降, 而BMAL1、REV-ERBα、PER1、PER2和RORA的表达显著上调, 提示生物钟参与肾透明细胞癌的发生发展[104], 但其具体机制尚未有报道. 尽管关于生物钟与肾脏肿瘤的研究还只处于萌芽阶段, 但结合生物钟紊乱可显著加速肝癌、肺癌等多种肿瘤发生发展的不争事实及其具体分子机制的逐渐明确[105], 我们有理由推测缓解生物钟紊乱也可能成为防治肾脏肿瘤的一个重要举措.

8 总结与展望

生物钟与肾脏功能稳态密切相关, 尽管已有数据提示环境干扰介导的生物钟紊乱会不同程度加速肾脏疾病的进程, 不同时间点手术操作也可能会对肾脏损伤预后造成显著差异等, 但现有研究的人群范围还相对局限, 部分结论尚存在争议, 因此进一步开展更大规模设计更完善的临床实验是阐明生物钟紊乱与肾脏疾病进程关系的必然趋势. 此外, 随着近年来生物钟基因敲除或突变等模式动物构建的日趋成熟, 从分子层面阐述生物钟与肾脏生理和疾病关系的研究日益增多(表1), 但作为全身表达节律基因第二丰富的组织器官, 相比肝脏而言, 肾脏生物钟的研究还相对匮乏. 考虑到肾脏细胞的高度异质性, 深入研究不同肾脏细胞的生物钟特征及其与疾病发展的关系对了解肾脏生物钟及其在机体内环境稳态调节中的作用的至关重要, 明晰中央主时钟和其他组织外周时钟在肾脏功能稳态调控中的关系也不可或缺. 此外, 临床应用中, 如何诊断或缓解生物钟紊乱是生物钟研究领域长期以来的难题, 考虑到不同时间点或时段收集尿液标本的高度可行性, 进一步通过高通量组学分析尿液昼夜节律相关指标, 将会为包括肾脏疾病在内的多种疾病的诊治提供极大便利. 从生物钟学相关的角度, 如缓解生物钟紊乱、时辰药理学应用, 或靶向特定生物钟分子, 防治临床重大肾脏疾病也是未来值得期待的方向.

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Summary for “肾脏功能稳态和损伤的生物钟调节机制”

Biological clock regulation in renal physiology and pathophysiology: from homeostasis to injury

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The kidneys play a pivotal role in maintaining fluid and electrolyte balance, blood pressure regulation and metabolic homeostasis in the body. These essential functions are intricately regulated by the circadian clock, an internal timekeeping system that aligns physiological processes with the 24-hour day-night cycle. Growing evidence has demonstrated that most renal physiological processes, including renal blood flow, glomerular filtration, tubular reabsorption, hormone secretion, among others, exhibit circadian fluctuations, underscoring the critical role of the circadian clock in maintaining normal renal function. Core clock genes, such as Bmal1, Clock, Per, and Cry, serve as pivotal components of these regulatory mechanisms, orchestrating the temporal coordination of renal physiological processes. For instance, they regulate the expression and activity of key transporter proteins in the kidney, including Na+/H+ exchanger 3 (NHE3), epithelial Na+ channels (ENaC), aquaporin 2 (AQP2), as well as other critical molecules. Additionally, circadian clock proteins modulate the renin-angiotensin-aldosterone system and endothelin signaling pathways, which are master regulators of blood pressure homeostasis. Importantly, disruptions in circadian rhythms—triggered by shift work, lifestyle factors, environmental stressors, genetic mutations, disease states, and so on—are increasingly recognized as key contributors to adverse renal outcomes, manifesting as reduced glomerular filtration rate, impaired sodium handling, and disturbances in metabolic and homeostatic processes, ultimately elevating the risks of chronic kidney disease (CKD), acute kidney injury (AKI), hypertension, and associated cardiovascular complications. Conversely, kidney diseases like CKD and AKI can disrupt circadian rhythms, indicating a reciprocal interplay between renal dysfunction and circadian regulation. Understanding this complex interplay between the circadian clock and renal pathophysiology may pave the way for developing targeted interventions for kidney diseases. Emerging evidence has highlighted the potential benefits of maintaining a consistent circadian rhythm to optimize kidney function and protect against renal diseases, highlighting the importance of synchronizing biological clocks for renal health. Chronotherapy, the practice of aligning medical interventions with the body’s biological rhythms, has also shown promise in improving treatments for kidney-related conditions. This review aims to summarize recent advancements in understanding the role of the circadian clock in renal physiological homeostasis and disease progression, with a particular focus on the mechanisms by which core clock genes influence kidney injury. Advancing knowledge in this area is crucial for translating chronobiological insights into effective strategies for preventing and treating kidney diseases, ultimately improving renal health and enhancing overall quality of life.

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