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Review article

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Disruption of circadian rhythm as a potential pathogenesis of nocturia

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Abstract

Increasing evidence suggested the multifactorial nature of nocturia, but the true pathogenesis of this condition still remains to be elucidated. Contemporary clinical medications are mostly symptom based, aimed at either reducing nocturnal urine volume or targeting autonomic receptors within the bladder to facilitate urine storage. The day–night switch of the micturition pattern is controlled by circadian clocks located both in the central nervous system and in the peripheral organs. Arousal threshold and secretion of melatonin and vasopressin increase at night-time to achieve high-quality sleep and minimize nocturnal urine production. In response to the increased vasopressin, the kidney reduces the glomerular filtration rate and facilitates the reabsorption of water. Synchronously, in the bladder, circadian oscillation of crucial molecules occurs to reduce afferent sensory input and maintain sufficient bladder capacity during the night sleep period. Thus, nocturia might occur as a result of desynchronization in one or more of these circadian regulatory mechanisms. Disrupted rhythmicity of the central nervous system, kidney and bladder (known as the brain–kidney–bladder circadian axis) contributes to the pathogenesis of nocturia. Novel insights into the chronobiological nature of nocturia will be crucial to promote a revolutionary shift towards effective therapeutics targeting the realignment of the circadian rhythm.

Sections

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Key points

- Growing evidence has shown that disrupted rhythmicity of the central nervous system, kidney and bladder (the brain–kidney–bladder circadian axis) contributes to the pathogenesis of nocturia.
- The daily rhythm of human behaviour and physiology is regulated by the transcription–translation feedback loop, which exists both in the brain and in peripheral metabolic tissues, consisting of opposite transcriptional activators (*CLOCK* and *BMAL1*) and repressors (*PER* and *CRY*).
- Disruption of the central clock in the suprachiasmatic nucleus and neuroendocrine system leads to nocturia through impaired sleep quality and misaligned release of hormones such as melatonin and arginine vasopressin.
- Most physiological renal processes, such as urine secretion and water reabsorption, follow a circadian pattern of activity; disruptions of this pattern can cause nocturia.
- The circadian expression of peripheral clock genes in the bladder leads to time-dependent variations of bladder sensation and excitability, which can be disorganized under pathophysiological conditions contributing to nocturia onset.
- Expanding knowledge of the molecular basis of circadian regulation and dysregulation within the brain–kidney–bladder circadian axis will help to develop strategies for the prevention, management and treatment of nocturia based on chronobiology.

Introduction

Humans have a set of well-orchestrated mechanisms to prevent nocturia, defined as waking up to urinate during the primary sleep period[1–3]. However, these intricate mechanisms are vulnerable during urological, nephrotic, neurological, endocrine, psychological and circulatory disturbances, causing nocturia and its related sequelae, including poor sleep, fatigue, reduced quality of life, depression or anxiety, bone fractures from falls, and increased risk of cardiovascular events and mortality[4–9]. Results from a 2013 review of 43 studies reporting nocturia prevalence estimated that up to 20% of individuals aged 20–40 years old, and 60% of individuals >70 years old need to void at least twice during the main sleep period[10]. Results from several subsequent surveys of community-based or hospital-based populations reported that among middle-aged and older people (>40 years old), 65–91% of men and 44–66% of women reported ≥2 voids per night despite some differences between the studies in definitions, outcome criteria and ethnic representation of participants[11–15].

In the past, nocturia has often been considered to be caused by an enlarged prostate or an overactive bladder (OAB)[16–18]. This concept has been questioned based on evidence that removal of the prostate (by either transurethral resection or radical prostatectomy) or conventional therapies for OAB do not eradicate nocturia in a considerable proportion of patients, suggesting the involvement of other pathophysiological factors[19–21].

Potential causes of nocturia

In general, nocturia might arise from one or more aetiologies including external triggers, changes in the rate of urine production during the sleep phase, or storage capacity of the urinary bladder.

Sleep disorders

A reciprocal relationship exists between sleep disorders and nocturia, as each of these conditions can be a trigger for the other[22,23]. Frequent awakening arising from nocturia disrupts the normal sleep cycle, particularly the restorative slow-wave sleep phase, which worsens the quality of life. This effect particularly affects old patients, who show increasing fragmentation of the sleep cycle, which is a risk factor for some systemic disorders, such as cardiovascular and metabolic disorders[24–27]. Nocturia is affected by external factors that disrupt the sleep cycle, such as obstructive sleep apnoea (OSA), insomnia, restless legs syndrome (also known as periodic limb movements), non-rapid eye movement parasomnias, or rapid eye movement sleep behaviour disorder[28]. These factors can reduce the brain arousal threshold or the depth of sleep, disrupting nocturnal urine production[28,29]. Furthermore, circadian dysregulation of these external factors can further fragment the sleep cycle, increasing the incidence of nocturia.

Much of the focus on primary sleep disorders and nocturia has been on the pathophysiology of OSA and nocturia. Increase in venous return induced by periodic raised inspiratory efforts associated with OSA is one mechanism that might act by inducing more negative intrapleural pressures, with a consequent increased release of atrial natriuretic peptide (ANP) and induction of a natriuresis[30,31]. This hypothesis is corroborated by the observation that continuous positive airway pressure ventilation to mitigate against OSA reduces the incidence of nocturia[32].

Nocturnal polyuria

Nocturnal polyuria is defined as an increase in nocturnal urine output by 20% in young adults (<25 years old), by 20–33% in middle-aged individuals (25–65 years old), and by 33% in those >65 years old[2,33–35]. Nocturnal polyuria is considered to be the major contributing factor to nocturia, accounting for 57–64% of nocturia instances[36]. Nocturnal polyuria is a heterogeneous condition that can arise as a result of high free water and high sodium clearance rate, either alone or in combination[37]. Nocturnal polyuria is associated with an array of systemic external factors including cardiovascular diseases, such as congestive heart failure and hypertension induced by salt retention; third-space fluid sequestration and dysregulated circadian secretion of arginine vasopressin (AVP, also known as antidiuretic hormone); or renal tubular dysfunction[7,33,34,38]. Nocturnal polyuria occurring in the absence of identifiable factors is known as nocturnal polyuria syndrome[37,39–42].

Global polyuria

Global polyuria is defined as a 24-h urine output ≥40 ml/kg (ref. 1). This condition might be caused by primary polydipsia, diabetes insipidus, pituitary tumours, hypopituitarism or some pharmaceuticals, such as diuretics, selective serotonin reuptake inhibitors, Ca^{2+} channel blockers, tetracycline or lithium[41,43,44].

Reduced nocturnal bladder capacity

The reservoir ability of the bladder can be affected either by a large residual volume, structural abnormalities (such as bladder outlet obstruction, bladder contracture and fibrosis) or functional deficiencies (such as OAB, underactive bladder, cystitis, bladder pain syndrome

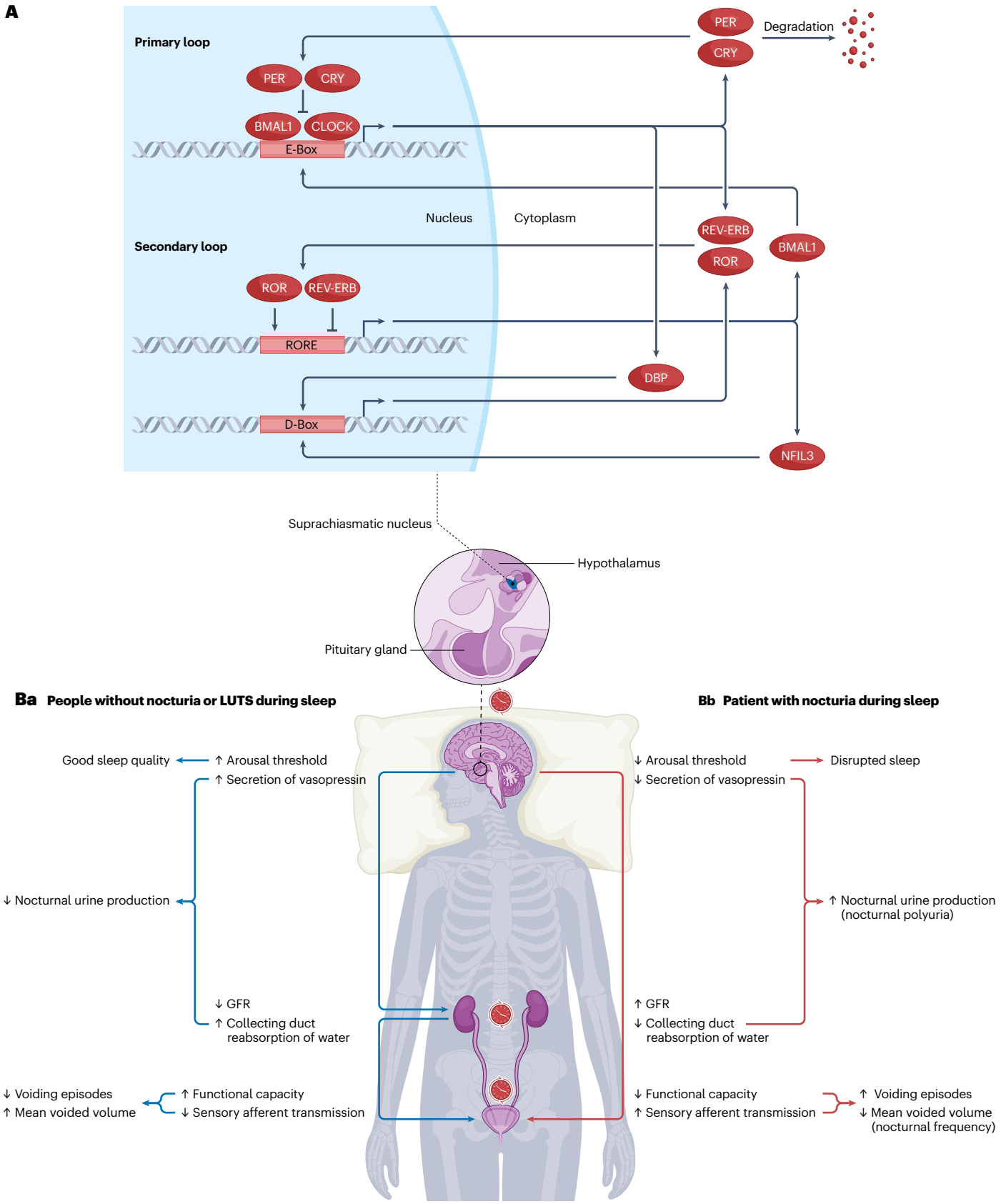

A
Primary loop
PER
CRY
BMAL1
CLOCK
E-Box
Degradation
Nucleus
Cytoplasm
Secondary loop
ROR
REV-ERB
RORE
REV-ERB
ROR
BMAL1
DBP
D-Box
NFIL3
Suprachiasmatic nucleus
Hypothalamus
Pituitary gland
Ba People without nocturia or LUTS during sleep
Bb Patient with nocturia during sleep
Good sleep quality
↑ Arousal threshold
↑ Secretion of vasopressin
↓ Nocturnal urine production
↓ GFR
↑ Collecting duct reabsorption of water
↓ Voiding episodes
↑ Mean voided volume
↑ Functional capacity
↓ Sensory afferent transmission
↓ Arousal threshold
↓ Secretion of vasopressin
Disrupted sleep
↑ Nocturnal urine production (nocturnal polyuria)
↑ GFR
↓ Collecting duct reabsorption of water
↓ Functional capacity
↑ Sensory afferent transmission
↑ Voiding episodes
↓ Mean voided volume (nocturnal frequency)

Fig. 1 | The transcription–translation feedback loop and the brain–kidney–bladder circadian axis. The central circadian pacemaker, located in the suprachiasmatic nucleus (SCN), is regulated by the transcription–translation feedback loop (TTFL), which mainly consists of a primary and a secondary loop (part **A**). In the primary loop, circadian locomotor output cycles kaput (CLOCK) and brain and muscle aryl hydrocarbon receptor nuclear translocator-like protein 1 (BMAL1) heterodimers bind to the E box of the promoters of the target genes period (*PER*) and cryptochrome (*CRY*) and induce their transcription. In a negative feedback fashion, the excessive production of PER and CRY proteins inhibits the transcriptional activity of CLOCK–BMAL1 and leads to the self-degradation of PER and CRY. Once the levels of PER and CRY drop to sufficient levels, CLOCK– BMAL1-mediated transcription can be restarted. In the secondary loop, the CLOCK–BMAL1 complex also induces the expression of the nuclear receptors REV-ERB, retinoid-related orphan receptor (ROR) and D-box binding protein (DBP). REV-ERB and ROR repress and activate the transcription of BMAL1, respectively, through binding to the ROR/REV-ERB response element (RORE). DBP activates D-box-dependent transcription, leading to the expression of ROR. This process can be inhibited by NFIL3, a transcriptional repressor that binds to D-box genes. NFIL3 transcription can be activated or repressed by the binding of REV-ERB and ROR to RORE, respectively. The TTFL also exists in multiple peripheral organs besides the SCN. Nocturia has been shown to have a chronobiological nature involving a set of autonomous but integrated circadian rhythmic mechanisms in the brain, kidney and bladder, which we refer to as the brain–kidney–bladder circadian axis (part **B**). In people without nocturia or lower urinary tract symptoms (LUTS) during sleep (part **Ba**), the brain sets up a high arousal threshold during the main sleep period to avoid external and internal disturbance. Vasopressin is periodically secreted from the posterior pituitary gland to promote the reabsorption of water in the collecting duct of the nephron. To further reduce urine production, the kidney has its own circadian pattern with a reduced glomerular filtration rate (GFR) during sleep. Bladder function also changes in a circadian fashion, with increased storage capacity and decreased sensory afferent transmission during the main sleeping hours to minimize the voiding episodes. Nocturia (part **Bb**) might arise from disruption in one or more of these circadian regulation patterns in the brain–kidney–bladder axis, which leads to sleep disorders, increased nocturnal urine production and reduced nocturnal bladder capacity.

and neurogenic bladder). This condition is usually characterized by increased nocturnal voiding episodes with a reduced mean void volume[41,43,44].

Current treatment of nocturia

The treatment of nocturia is usually tailored around existing pathophysiological changes, which are determined through clinical assessments including medical history, physical examination, bladder diary, laboratory tests and imaging studies. Lifestyle advice and behavioural modifications are recommended to all patients as a first-line treatment[2,33,34,44–46]. These modifications include restricting fluid consumption before sleep, which might help to minimize urine production[46,47]; avoiding caffeine and alcohol intake, which could be beneficial in reducing bladder sensitivity[47–49]; aerobic exercise to improve night-time sleep quality[46,47]; bladder retraining, which can restore functional bladder capacity[50]; reducing peripheral oedema with compression stockings and leg elevation[51]; and maintaining continuous positive airway pressure for patients with OSA[52].

If no symptom remission is observed with these behavioural strategies, medications are needed to reduce nocturnal urine production. Desmopressin (which is a synthetic replacement for AVP) might be effectively used to promote the reabsorption of water from the distal tubule and collecting ducts of the nephron during the night[2,41,43,44,46,53]. Medications for OAB including antimuscarinics and β3-adrenergic agonists can also be prescribed to reduce bladder sensation and detrusor overactivity[53]. Diuretics taken at bedtime to facilitate the expulsion of accumulated fluids during daytime increase nocturia, but, in some patients, especially those with hypertension and lower limb oedema, taking diuretics in the afternoon effectively reduces nocturnal voids and urine volume, owing to the discharge of salt and water before sleeping[53,54]. In male patients with an enlarged prostate and voiding dysfunction, α1-adrenergic antagonists, 5α-reductase inhibitors and phosphodiesterase 5 inhibitors can be useful to facilitate bladder emptying[2,41,43,44,46]. These pharmaceuticals can be used alone or in combination, depending on each patient's co-existing conditions.

Regulatory mechanisms of the circadian rhythm

Multiple therapeutic options are available for nocturia working by reducing either voiding episodes or nocturnal urine volume, but many patients remain refractory to treatment, mainly owing to the heterogeneous nature of nocturia pathogenesis. The aetiology of nocturia is multifactorial, and can be attributed to disruptions in the rhythms of sleep–wake cycles, urine production and bladder capacity. Thus, nocturia can be understood by having a comprehensive perspective of rhythm disturbances. Results from studies on the circadian rhythmic nature of daily urine excretion in healthy children and young adults showed that up to 75% of total urine output occurs during the daytime, with a major peak between 6 pm and 10 pm (refs. 55,56). This rhythm is strikingly different in older women and men with nocturia, with a peak rate of diuresis shifting towards late hours, during the sleep phase of the cycle[57]. Nocturia has been shown to have a chronobiological nature involving a set of autonomous but integrated circadian rhythmic mechanisms in the brain, kidney and bladder, which we refer to as the brain–kidney–bladder circadian axis. Sleep disorders, irregular lifestyle, neurodegenerative diseases and metabolic diseases are all associated with circadian disruption as well as nocturnal polyuria and increased urinary frequency. Thus, understanding the role of circadian axis disruptions as a potential cause of nocturia is imperative[2,58,59].

In this Review, we introduce the molecular mechanisms of the circadian clock regulatory cycle and discuss how desynchronized circadian rhythms of the brain, kidney and bladder might contribute to nocturia.

Regulation of the circadian rhythm — transcription–translation feedback loop

The daily rhythm of human behaviour and physiology is regulated by the transcription–translation feedback loop (TTFL), which exists in both the brain and peripheral metabolic tissues[60–62] (Fig. 1). The TTFL mainly consists of a primary and a secondary cycle in which the transcription of promotive and repressive clock genes oscillate in an autoregulatory fashion with a repeated cycle of 24 h in synchrony with the solar day[60,63–65]. A master circadian pacemaker located in the hypothalamic suprachiasmatic nucleus (SCN) synchronizes the rhythm of other central nucleus components, whereas peripheral tissues set their own autonomous circadian clocks, which are integrated to synchronize their pace with the core clock[60,62,66].

In the primary loop, the active components of the TTFL are heterodimers of the transcription factors brain and muscle aryl hydrocarbon receptor nuclear translocator-like protein 1 (BMAL1) and circadian

locomotor output cycles kaput (CLOCK)[60]. The CLOCK–BMAL1 heterodimer binds to the E box of the *cis*-promoter and enhancer regions of the period 1 (*PER1*), period 2 (*PER2*), cryptochrome 1 (*CRY1*) and cryptochrome 2 (*CRY2*) genes, inducing transcription of these genes[67] (Fig. 1A). The accumulation of PER and CRY proteins to a certain concentration will lead to dimerization and translocation into the nucleus, where these proteins bind to CLOCK–BMAL1 complexes and repress CLOCK–BMAL1-mediated transcription[67]. PER and CRY proteins also undergo a number of post-translational modifications, resulting in a proteasome-induced 24-h rhythmic degradation, which reboots CLOCK–BMAL1-mediated transcription, keeping the cycle running[60].

In the secondary loop, the CLOCK–BMAL1 complex induces transcription of the nuclear receptors retinoid-related orphan receptor (ROR, including RORα, RORβ and RORγ) and REV-ERB (REV-ERBα and REV-ERBβ)[60] (Fig. 1A). REV-ERB and ROR subtypes compete for binding to REV-ERB–ROR response elements in the promoter and enhancer regions of target genes, with REV-ERB repressing and ROR activating transcription of BMAL1 (ref. 67).

Circadian rhythm-mediated regulation of physiological functions

The hierarchical organization of the circadian system, from the master pacemaker to extra-SCN clocks, regulates multiple physiological functions. For example, blood pressure follows a circadian pattern characterized by increased blood pressure during wakefulness and decreased blood pressure during sleep[68]. In healthy individuals, plasma glucose tolerance also undergoes time-dependent variations, with an increase in the morning and a decrease in the evening, and correlates positively with rhythmic pancreatic insulin secretion[69]. Adipocytes have their own peripheral clock coordinated with the central pacemaker to regulate lipid metabolism by regulating the expression of several crucial enzymes for lipolysis, such as adipose triglyceride lipase, lipoprotein lipase and hormone-sensitive lipase[70].

Some circadian regulation mechanisms are also involved in regulating the timing of urine production and voiding behaviour. For example, strengthening of synaptic connections following synaptic high-frequency stimulation, which leads to memory formation and long-term potentiation, is closely regulated through the circadian oscillation of proteins of the cyclic AMP–mitogen-activated protein kinase–cAMP responsive element-binding proteins (cAMP–MAPK–CREBP) pathway, as well as through circadian variation of *N*-methyl-D-aspartate receptor-evoked calcium current in central neurons[71–73]. Both MAPK and glutamatergic signalling were shown to participate in bladder sensory and nociception input, suggesting potential circadian features of these molecules in regulating rhythmic bladder function[74–77].

A bidirectional connection also exists between circadian genes and metabolic pathways, in both central and peripheral tissues. Glycogen and fatty acid synthesis peaks during the feeding period, whereas the plasma level of total amino acids and oxidative metabolism peak during fasting, and this regulation is primarily accomplished through circadian rhythm-dependent expression of crucial enzymes[63,65,78–80]. For example, in glucose metabolism, peak levels of glucokinase and the hepatic glucose transporter protein GLUT2, which promote glucose storage by facilitating glycogenesis, coincide with feeding; whereas protein kinase A, which promotes glycogenolysis and gluconeogenesis to supply glucose, reaches expression peaks during fasting[63]. The oscillatory homeostasis of glucose might in turn influence transcription of clock genes within SCN pacemaker neurons and communication pathways between SCN and extra-SCN neurons, as neuronal projections originating in the SCN directly synapse in the lateral hypothalamic area, which consists of neurons important in peripheral glucose metabolism[81]. The adenosine monophosphate-dependent protein kinase sirtuin 1 and the mammalian target of rapamycin (mTOR) also participate in both glucose metabolism and circadian oscillations of SCN and extra-SCN neurons[81]. Metabolic balance is an essential element in maintaining normal lower urinary tract function. Thus, circadian integration of metabolism can be hypothesized to be connected with nocturnal voiding behaviour.

Dysregulation of circadian rhythm in pathophysiological conditions

Off-cycle exposure to environmental cues can disrupt circadian homeostasis and have detrimental effects on human behaviour, including sleep–wake cycles and rest–activity rhythms, and health conditions. For instance, shift workers or travellers who experience rapid changes in time zones are prone to suffering from rhythmic desynchrony, which can produce a vicious cycle contributing to a series of metabolic, endocrine and cardiovascular disorders such as obesity, insulin resistance, disrupted cortisol rhythms and increased blood pressure[81–84]. Similarly, sleep deprivation, poor sleep quality and narcolepsy substantially dampen the rhythmic expression of clock genes, and are associated with diabetes, metabolic syndrome and obesity[81,85,86]. Exercise protocols with a specific timing can improve sleep quality and facilitate the adaptation to work shifts, in turn ameliorating the negative metabolic consequences of this lifestyle[83]. Inverted sleep–wake cycles and insomnia are both important risk factors for nocturia[28]. Conversely, frequent nocturnal urination might contribute to dysregulated circadian sequalae, such as circadian blood pressure variation and depressive symptoms[5,87,88]. Lengthening the first uninterrupted sleep period through oral intake of low-dose desmopressin might be beneficial to reduce blood glucose levels in patients with nocturia[89]. Together, this evidence highlighted the role of dysregulated circadian rhythms as a contributing factor for nocturia and also as a potential target for treatment[28,90].

Circadian rhythm disturbance is a manifestation of neurodegenerative diseases, and could also be a risk factor for developing Alzheimer disease and related dementia, as well as Parkinson disease[91]. For example, patients with moderate-to-severe Alzheimer disease are prone to having inverted rest–activity patterns, increased levels of sleep fragmentation, and depleted secretion of melatonin, vasoactive intestinal polypeptide, AVP and neurotensin, possibly owing to the loss of crucial neuronal populations in the SCN[91,92]. Conversely, results from several longitudinal studies with long-term follow-up monitoring suggested that older individuals (≥65 years old) with a reduced amplitude of circadian rhythms and circadian phase shifts, such as less consolidated night-time sleep patterns, experienced increased daytime napping and cognitive decline, preceding the risk of developing neurodegenerative diseases[93–96]. Additionally, aberrant DNA methylation of *BMAL1* and subsequent disruption of the rhythmic transcription of this gene were identified in postmortem frontal cortex samples from patients with Alzheimer disease, indicating that epigenetic deregulation of circadian rhythms might contribute to cognitive impairment and neurodegeneration[97]. Coherent with these results, *Bmal1*-deficient mice showed neurological phenotypes including severe spontaneous astrocyte proliferation, increased neuroinflammation, oxidative damage and synaptic degeneration, together with impaired functional brain connectivity, learning and memory[98]. In addition to the reciprocal

relationship between circadian disruption and neurodegenerative diseases, mice harbouring modifications in various types of clock genes showed changes in the circadian rhythm of urination, including disruptions in diurnal rhythms of neuroendocrine function, urine production and bladder capacity[99–103] (Table 1). This evidence suggests that disrupting clock gene expression might be associated with both neurodegenerative diseases and nocturia.

Dysregulation of circadian rhythm of the central clock as a potential cause of nocturia

A central clock in the SCN controls the body's circadian rhythms and synchronizes peripheral clocks in most organs, tissues and cells through the autonomic nervous system, hormonal signals and behavioural control[62]. Disruption of the central clock in the central nervous system and neuroendocrine system can affect lower urinary tract function.

Many pathologies including cardiovascular disorders, pulmonary dysfunction and hepatic failure, as well as ageing, are associated with increased nocturia[42,104–107], suggesting a common mechanism. Furthermore, in healthy older individuals, loss of circadian rhythmicity of AVP secretion, as well as increased plasma levels of natriuretic peptides, increases nocturia[108–110]. Desynchronization of circadian rhythmicity in the central nervous system has also been suggested to be a potential contributor to nocturia in individuals with metabolic disorders or those experiencing disruption of sleep[81,111].

Circadian regulation of suprachiasmatic nucleus hormones in nocturia — melatonin and arginine vasopressin

The SCN acts as an intrinsic central clock with a period of ~24 h, communicating with other brain centres and with peripheral tissues through the neuroendocrine system or through projections to both branches of the autonomic nervous system[62,66]. Circadian rhythm controls the specific functions of different tissues but also general tissue metabolism and sleep, which in turn regulate SCN activity through a feedback loop[81,111]. The extent of communication between the peripheral and the central clock depends on the integration of input signals and environmental cues, which have the ability to reset the magnitude and phase of the central clock and, in turn, modulate output signals. The SCN can be regulated by photic input from the retina and non-photic inputs[66].

SCN receiving photic input from the retina enters a light–dark cycle, in which a synchronized SCN output pathway through the sympathetic superior cervical ganglion projects to the pineal gland to release the tryptophan derivative melatonin[62]. Regulation by the central clock increases melatonin secretion in the dark phase. Among the sites of action of melatonin is also SCN, where melatonin binds to G-coupled MT1 and MT2 receptors, with the effect of promoting sleep and fatigue-like states and, ultimately, reducing urine output[112–114]. Slow-release melatonin preparations, such as circadin or MT1 and MT2 receptor agonists, have been used for nocturia treatment in

Table 1 | Clock gene abnormalities along the brain–kidney–bladder circadian axis in relation to nocturia

Location	Clock genes	Proposed influence on nocturia
Brain	*Bmal1*	Overexpression of *Bmal1* obliterated the circadian rhythm of melatonin secretion[114] Paraventricular nuclei-specific *Bmal1* ablation suppressed the expression of AVP during the daytime, resulting in a reduction in plasma AVP concentration[130]
Brain	*Clock*	The interactions between *Clock* and *HIFa* induce the expression of *AVP* expression[144]
Brain	*Per1* and *Per2*	*PER1* is rhythmically expressed in the pineal body as one of the regulators of melatonin synthesis[266,267]
Brain	*Cry1* and *Cry2*	Suppression of *AVP* expression and arrhythmia were observed in *Cry1* and *Cry2* double-knockout mice[268]
Kidney	*Bmal1*	Ablation of *Bmal1* expression in renin-secreting granular cells disrupts the circadian pattern of renin protein expression in kidney tissue and results in a moderate reduction of plasma aldosterone levels[164] Deletion of *Bmal1* in podocytes results in loss of circadian rhythmicity of the glomerular filtration rate, along with disruption of the circadian patterns of urinary creatinine, Na^+, K^+ and water excretion, and the diurnal pattern of plasma aldosterone levels[165]
Kidney	*Clock*	*Clock*-null mice showed loss of circadian rhythm in plasma aldosterone levels, as well as in urinary Na^+, K^+ and water excretion[159,162]
Kidney	*Per1* and *Per2*	*Per1* regulates several genes encoding crucial proteins involved in solute reabsorption along the nephron, including ENaC, Na^+–Cl^- co-transporter, the Na^+–glucose co-transporter, and Na^+–K^+-ATPase positive regulator[168,170–172] *Per1* and *Per2* double-knockout mice showed disturbed circadian rhythm in urine production[103] Following global or kidney-specific *Per1* deletion, renal *ET1* gene expression and inner medullary ET1 peptide levels increased, suggesting that *Per1* negatively regulates the endothelin axis in the kidney[172,175]
Kidney	*Cry1* and *Cry2*	Global *Cry1* and *Cry2* deletion result in increased plasma aldosterone level and reduced circadian aldosterone oscillations[161]
Bladder	*Bmal1*	The circadian rhythmic expression of *Bmal1* is regulated by the glucocorticoid receptor signalling pathway in a concentration-dependent and time-dependent manner in the human urothelium[221]
Bladder	*Clock*	*Clock*-mutant mice lose circadian variations in urine volume voided per micturition[102]
Bladder	*Per1* and *Per2*	The circadian expression of intrinsic *Per2* correlated positively with detrusor contractile response to carbachol, suggesting the participation of clock genes in rhythmic bladder function[203] *Per2* expression and response to mechanical stimulation are substantially reduced with ageing, which might contribute to age-related bladder dysfunctions[203]
Bladder	*Cry1* and *Cry2*	*Cry*-null mice show no circadian rhythms in urine volume voided per micturition[101]
Bladder	*Rev-Erba*	*Rev-Erba* regulates the transcription of connexin 43, a gap junction protein responsible for diurnal variation in bladder sensitivity and capacity[101]

AVP, arginine vasopressin; BMAL1, brain and muscle aryl hydrocarbon receptor nuclear translocator-like protein 1; CLOCK, circadian locomotor output cycles kaput; CRY, cryptochrome; ENaC, epithelial sodium channel; ET1, endothelin 1; PER, period.

several clinical trials[115]. As observed in a study in rats, the possible mechanism of action of melatonin in this context could be the activation of the inhibitory γ-aminobutyric acid receptor, leading to increased bladder capacity and decreased urine volume[116,117]. Results from a cross-sectional observational study showed higher urinary 6-sulfatoxymelatonin concentration in the older population (≥60 years old) with nocturia than in age-matched individuals without nocturia, suggesting an inverse correlation between melatonin secretion and nocturia[118]. Thus, melatonin supplement could be a potential therapeutic option, as shown in a randomized clinical trial in which a 2-week oral intake of melatonin (2 mg/day) significantly alleviated nocturia (−1.0 (−3.0 to 0.0) versus 0.0 (−2.3 to 1.3) episodes per night; $P < 0.001$) and increased median duration of the first uninterrupted sleep (1.0 (−0.3 to 4.5) versus 0.0 (−3.0 to 2.3) h; $P < 0.001$) compared with patients receiving placebo[119]. Similarly, in patients with neurological conditions such as Parkinson disease, treatment with melatonin significantly reduced nocturia episode ($P = 0.013$) and symptom scores ($P = 0.01$)[120]. However, in another trial including patients with multiple sclerosis, a similar dosage of circadin (2 mg/day) did not significantly alter nocturia episodes (1.4/night after melatonin treatment compared with 1.6/night in the placebo group; $P = 0.85$), suggesting that further validation is needed to determine the clinical value of this therapy[121].

AVP has a dual role in the context of controlling urine output. AVP is synthesized in magnocellular neurons of the hypothalamic supraoptic and paraventricular nuclei and is transported along neurons in the hypothalamic–hypophyseal tract to the posterior pituitary gland, from where AVP is secreted in response to changes in plasma osmolality[122]. Secreted AVP regulates water reabsorption at the collecting duct by increasing cell-surface expression of aquaporin 2 (AQP2) channels on the cell membrane of collecting duct cells[123]. AVP release follows a pronounced circadian rhythmicity, especially in young individuals (with a mean age of 25 years old), with a nadir in the late afternoon and a peak at night[110]; thus, the anti-diuretic effect of AVP helps to regulate nocturnal urine volume[124]. Additionally, ~20% of SCN neurons contain AVP-positive neurons, which show circadian rhythmic *AVP* mRNA expression with a peak during daytime, and also contain the E-box element in the AVP promoter region (the target of *CLOCK* and *BMAL1* transcription factors)[125,126]. The SCN then outputs to the magnocellular neurosecretory cells in the paraventricular nucleus through AVP-immunoreactive synapses, which synchronize the central clock and circadian AVP humoral release[126,127]. Thus, disruption of clock-guarding genes and circadian activity would affect the circadian pattern of plasma AVP levels, causing dysregulated water reabsorption and increased urine output during the sleep period. Proper AVP secretion and regulation is, therefore, important for normal circadian urinary function, and disruption of these processes can cause urinary dysregulation leading to nocturia[128–130].

Circadian misalignment during sleep disorders and central nervous system hypoxia in nocturia

Results from several studies have shown that reduced sleep quality, assessed objectively or subjectively, is associated with an increased incidence of nocturia[131,132]. Furthermore, shift workers experience an increased incidence of nocturia[133,134]. Sleep deprivation generates increased salt and water excretion at night, mainly related to dysregulation of the renin–angiotensin–aldosterone system (RAAS)[135]. Disrupted sleep quality, even increasing overall sleep duration, is also associated with nocturia[136]. However, responses to stress through dysregulation of circadian rhythms can be variable, making it difficult to identify causative mechanisms. The idea that some individuals experience high sleep reactivity (which refers to the degree of sleeping difficulty under stress) has been proposed as an explanation for the variability of disordered sleep patterns in relation to stress exposure, but how sleep reactivity influences the variability in the incidence of nocturia remains to be explored[137].

The relationship between OSA and nocturia has been extensively studied. OSA is a common condition induced by intermittent collapse of the upper respiratory tract during sleep, accompanied by periods of hypoxaemia, and is considered a risk factor for nocturia secondary to nocturnal polyuria[30,138]. Furthermore, OSA and nocturia share dominant demographic risk factors, such as advancing age and high BMI[139]. Thus, not surprisingly, treatment of OSA with continuous positive airway pressure ventilation substantially reduces nocturia episodes[139]. However, the relationship between OSA and nocturia is not exclusive, as nocturnal polyuria is independently associated with changes in circadian variation of extracellular fluid volume[140]. Additionally, chronic obstructive pulmonary disease with concomitant hypoxaemia is also associated with a prevalence of nocturia as high as that reported with OSA. Overall, ~15% of patients with chronic obstructive disease have OSA as a co-morbidity, and this condition is known as overlap syndrome[107]. The incidence of nocturia is significantly higher in patients with the overlap syndrome (63.5%) than in patients with OSA alone (63.5% versus 58.0%, $P < 0.01$), but patients with the overlap syndrome are also substantially older (mean age of 63.5 and 56.9 years old in the overlap syndrome and the OSA groups, respectively)[107]. Thus, to date, whether the presence of either of these two pulmonary disorders is an additional risk factor for nocturia for patients with either disorder alone is unclear.

A hallmark of tissue hypoxia is the activation of hypoxia-inducible factors (HIFs)[141]. HIFs are a family of transcription factors that form dimers consisting of an oxygen-regulated subunit (HIFα) and a constitutively expressed subunit (HIFβ), and encode genes that lead to restoration of tissue normoxia[141]. HIFα and clock proteins are members of the same transcription factor superfamily and together can synergistically enhance the expression of target genes, and can also generate circadian rhythm misalignment as a result of hypoxia variations at different times of the day[142,143]. Specifically, in the SCN, HIFα and *CLOCK* cooperate to promote transcription of AVP[144]. Hypoxia was hypothesized to desynchronize the circadian rhythm of AVP secretion, which is increased in the sleep phase normally, but results from human studies were conflicting. In a small study including four patients with post-stroke nocturia and nocturnal polyuria, the normal circadian rhythm of plasma AVP concentration was absent, as measured every 4 h from 8 am to 8 am the next morning[106]. However, in another study including patients with and without OSA, nocturnal secreted AVP, assessed through a single early morning urinary AVP measurement (normalized to the creatinine value) taken at 6 am, was similar in both groups (6.7 pg/ml/Cre in the OSA group versus 6.8 pg/ml/Cre in the non-OSA group, $P = 0.36$)[109]. Large trials are needed to determine the link between diurnal AVP secretion, hypoxaemia and nocturnal polyuria.

Dysregulation of circadian rhythm of renal function as a potential cause of nocturia

Most physiological renal processes follow a circadian pattern of activity, such as urine secretion and water reabsorption, in response to the rhythmic fluctuation of blood pressure, electrolytes and hormones[145,146]. Disturbance of the renal circadian rhythms is increasingly recognized as a risk factor for nocturia, suggestive of nocturnal polyuria.

Physiology of rhythmic renal function

In healthy humans, the glomerular filtration rate (GFR) oscillates between 120 ml/min and 90 ml/min, reaching a peak in the waking phase at ~2–3 pm, and a minimum during the middle of the sleep phase[147]. Na^+, K^+ and Cl^- excretions peak between 9 am and 12 pm, and then progressively decrease during the night-time[148]. Urine production follows a similar pattern, with increased volumes during the day and lowest during the night[146]. Regulators of salt and water excretion, such as the hormones AVP and aldosterone, show a circadian pattern of activity[146]. AVP plasma levels are higher at night than during the day, which helps to regulate nocturnal urine volume[124]. Aldosterone is secreted in response to variations in blood pressure and volume, as well as in plasma Na^+ levels, and primarily regulates Na^+ reabsorption through the epithelial sodium channel (ENaC) in the distal nephron[149]. In humans, plasma aldosterone levels show a diurnal pattern that parallels that of the GFR, peaking in the first half of the day and reducing to a nadir in the middle of the night[150].

This rhythmicity of renal function was initially thought to be a reaction of the kidneys to control water and solute balance in the body and maintain homeostasis in response to changes in circadian activity or changes in food and water intake[151]. This view was challenged by evidence that renal excretory rhythms can still persist for several days after periodic behavioural activity was switched, or fluid and food intake were controlled, or in conditions in which diurnal activity and feeding cycles were inverted[152–156]. This evidence generated the hypothesis that the rhythmicity of renal function is a self-sustained mechanism that might enable the kidney to anticipate the predictable circadian challenges to homeostasis[151]. The molecular basis of this mechanism remained elusive until the discovery of the mammalian circadian clock system.

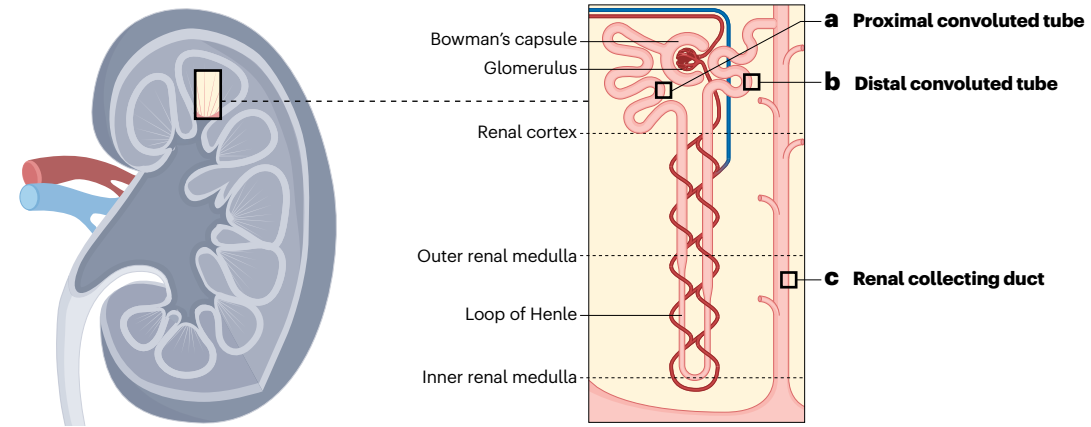
Potential molecular mechanisms underlying rhythmic renal function

Hundreds of putative clock-controlled genes have been identified throughout the nephron[157]. Rhythmic transcription has been identified for several crucial genes involved in renal salt and water transport, including genes encoding ion channels and receptors, such as the Na^+/H^+ exchanger 3 (NH3, encoded by *SLC9A3*), the α-subunit of epithelial Na^+ channels (α-ENaC, encoded by *SCNN1A*), aquaporins (AQP1, AQP2 and AQP3) and renal AVP receptors (V1AR and V2R)[146,158].

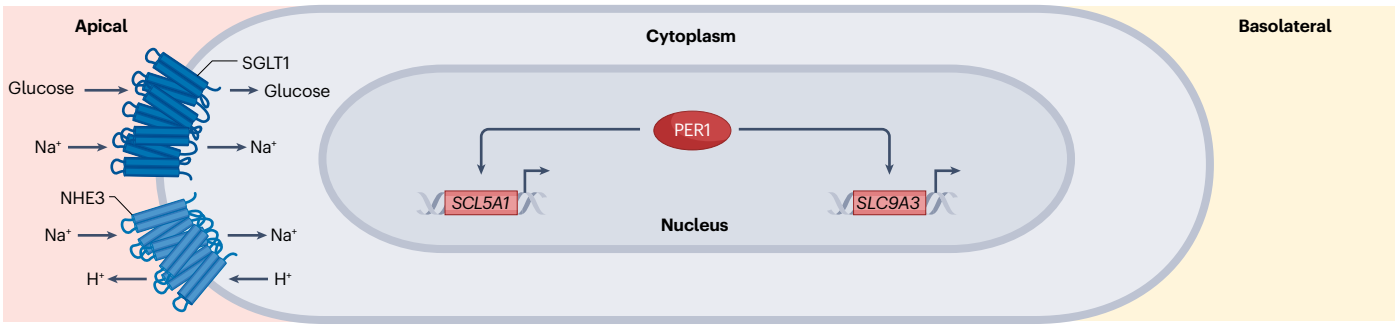
Disruption of the circadian clock through genetic ablation of different clock genes results in profound changes to the kidney transcriptome and to the rhythmicity and regulation of renal function[151,157–160]. For example, in mice with global *Cry1* and *Cry2* deletion, plasma aldosterone levels were significantly increased at both circadian time 0 and 12 ($P < 0.01$), and circadian aldosterone oscillations were enhanced compared with wild-type mice[161] *Clock*-null mice also showed disruption in the circadian rhythm of plasma aldosterone levels, reduction of circadian rhythmicity of urinary Na^+, K^+ and water excretion, and a substantial reduction in blood pressure[159,162]. Results from other studies showed that *Clock*-null mice also had altered circadian rhythm of 20-hydroxyeicosatetraenoic acid (20-HETE) synthesis in the kidney, leading to both a delayed shift in the acrophase (peak point of the cell cycle) and reduced average 24-h levels of 20-HETE[162]. Endogenous 20-HETE, released into the renal microcirculation, is a powerful regulator of renal tonus, Na^+ reabsorption and K^+ secretion, and modulates both the myogenic and the tubuloglomerular feedback-mediated regulation of glomerular filtration[163]. Results from studies in mice in which clock genes were selectively deleted in the kidney further highlighted the influence of the circadian clock on the modulation of the expression of RAAS components and other regulatory mechanisms[164]. Specifically, ablation of *Bmal1* in renin-secreting granular cells in mice disrupted the circadian pattern of renin protein expression in kidney tissue and resulted in a moderate reduction of plasma aldosterone levels[164]. Further analysis of these mice showed an increased GFR and urine volume and changes in the circadian rhythm of urinary Na^+ excretion, suggesting that local renal circadian clocks control body fluid homeostasis[164].

Ablation of *Bmal1* in podocytes (which are highly specialized glomerular cells essential for protein retention during glomerular filtration) in mice resulted in loss of the circadian rhythmicity of the GFR[165]. In these mice, disruption of GFR circadian rhythmicity was accompanied by substantial changes to the circadian patterns of urinary creatinine, Na^+, K^+ and water excretion, and by a dysregulation of the diurnal pattern of plasma aldosterone levels[165]. These findings highlighted the importance of peripheral kidney circadian clocks in regulating renal function oscillations. Conversely, in another study, the ablation of *Bmal1* in renal tubular cells in mice did not result in obvious abnormalities in renal Na^+, K^+ or water handling[166]. The fact that renal excretory rhythms were not affected by the inactivation of the molecular clock in renal tubular cells indicates that these rhythms are mainly regulated by external circadian time cues. One of these cues is probably diurnal oscillations in aldosterone levels. Aldosterone-mediated regulation of renal tubular Na^+ reabsorption involves multiple mechanisms that include regulation of ENAC expressed on the apical membrane of principal cells in the collecting duct[167]. *SCNN1*, the gene encoding α-ENaC, is regulated by *PER1* (ref. 168). Results from an in vivo study in *Per1* knockout mice have shown downregulation in *ENAC* expression, along with increased concentration of sodium in the urine and reduced blood pressure compared with wild-type mice[168]. *PER1* expression is positively regulated by aldosterone[168]. Upregulated *PER1* expression was observed in an aldosterone-stimulated renal collecting duct cell line and in the kidney of aldosterone-treated rats through mineralocorticoid and glucocorticoid receptor-mediated signalling[169]. Together, evidence that *PER1* is regulated by aldosterone and regulates ENaC suggest a role for *PER1* in mediating the downstream effects of aldosterone on ENaC in the renal collecting duct cells[168] (Fig. 2). *PER1* also regulates the expression of several other genes encoding crucial proteins involved in solute reabsorption along the nephron (Fig. 2), including the Na^+–Cl^- co-transporter (NCC, encoded by *SLC12A3*) and its regulatory kinases with-no-lysine kinases 1 and 4 (WNK1 and WNK4), the NHE3 and the Na^+–glucose co-transporter (SGLT), the Na^+–K^+-ATPase-positive regulator FXYD domain-containing ion transport regulator 5 (FXYD5), and the negative regulators of ENaC caveolin 1 and ubiquitin-conjugating enzyme E2 E3 (UBE2E3)[168,170–172].

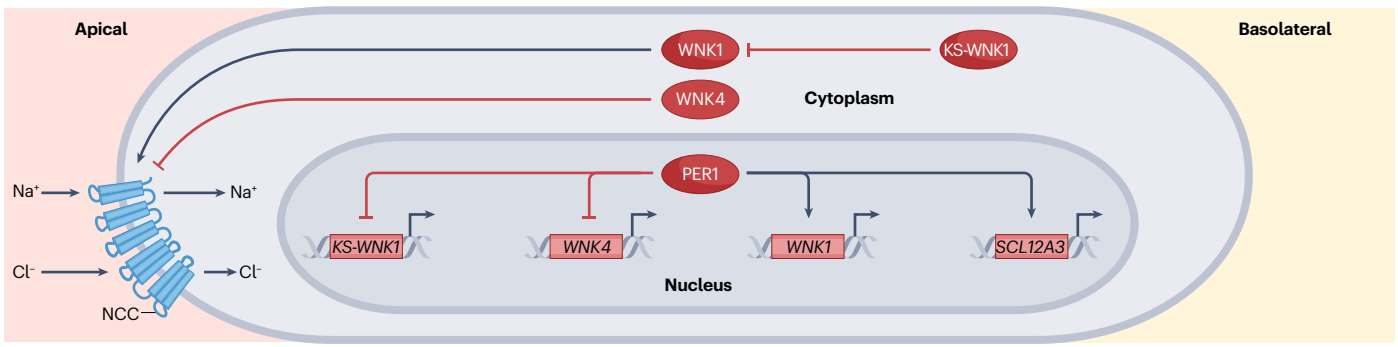
The endothelin 1 (ET1) axis in the kidney is also influenced by *PER1* (refs. 172,173) (Fig. 2). Endothelin regulates Na^+ handling in the collecting duct mainly through the activation of endothelin receptors type B[174]. These receptors inhibit renal tubular Na^+ reabsorption and promote Na^+ excretion in response to an increased NaCl intake, through MAPK-mediated ENaC phosphorylation, which reduces both ENaC activity and number[175]. In mice with global or kidney-specific *Per1* deletion in the distal nephron and collecting duct, renal *Et1* expression and inner medullary ET1 peptide levels increased, suggesting that *Per1* negatively regulates the endothelin axis in the kidney[146,158,172,175]. Coordination of these opposite effects of aldosterone and ET1 on Na^+ handling in the kidney is another example of how the circadian clock regulates and drives the rhythmicity of renal function.



a Proximal convoluted tube cell



b Distal convoluted tube cell



c Renal collecting duct cell

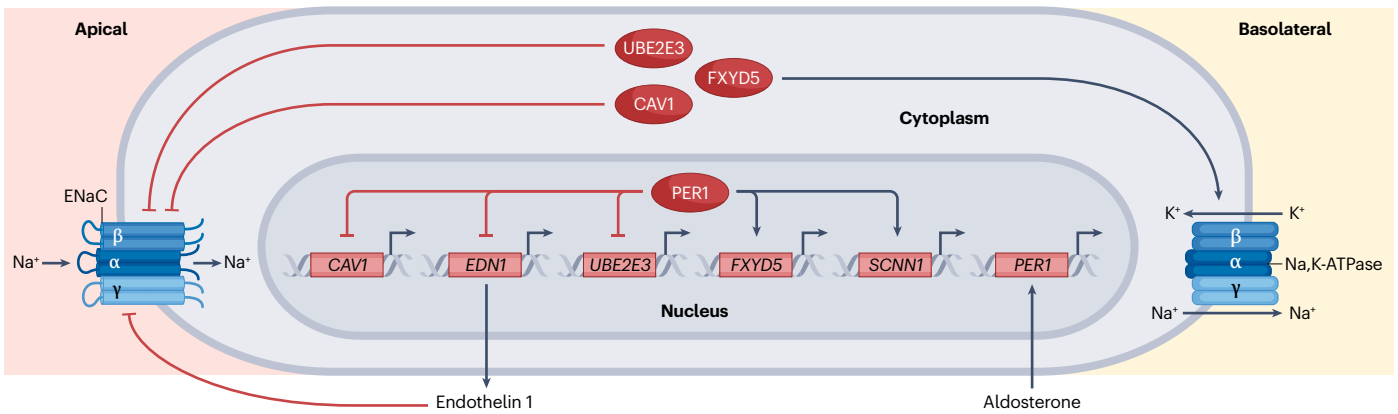


Fig. 2 | PER1-mediated circadian control of the nephron. Period 1 (PER1) was shown to be involved in the transcriptional regulation of genes encoding crucial proteins modulating solute reabsorption along the nephron. **a**, In proximal tubule cells, PER1 positively regulates the expression of *SLC5A1* and *SLC9A3* (encoding the sodium–glucose co-transporter 1 (SGLT1) and Na^+/H^+ exchanger 3 (NHE3), respectively)[171]. **b**, In distal tubule cells, PER1 regulates the expression levels of *SLC12A3* (encoding the Na–Cl co-transporter (NCC)), and of genes encoding components of the with-no-lysine kinase (WNK) pathway, such as WNK1, WNK4 and KS-WNK1 (a kidney-specific WNK1 isoform), which regulate NCC activity[133]. **c**, In collecting duct cells, PER1 regulates the expression of the Na-K-ATPase-positive regulator FXYD domain-containing ion transport regulator 5 (FXYD5), in turn modulating this Na-K-ATPase activity. Additionally, PER1 regulates the activity of the epithelial sodium channel (ENaC), both by regulating the expression of *SCNN1*, which encodes the α-ENaC subunit, and of *UBE2E3* and caveolin 1 (*CAV1*), which are negatively regulators of ENaC. PER1 also negatively regulates the expression of *END1*, encoding endothelin 1, which is a negative regulator of ENaC. In the collecting duct cells, PER1 is also positively regulated by aldosterone and mediates the downstream effects of aldosterone on ENaC. UBE2E3, ubiquitin-conjugating enzyme E2 E3.

Potential role of desynchronized renal rhythmicity in nocturnal polyuria

In healthy individuals, nocturnal polyuria commonly develops with ageing and is the major factor contributing to nocturia[176]. With advancing age, circadian rhythms of diuresis-regulating hormones are dysregulated, and the concentrating capacity and the ability of kidney to retain Na^+ are reduced[108,110,177–179]. Similar to hormones, several genes involved in renal salt and water transport also show a circadian pattern of expression and activity that influences renal rhythmicity[146,158]. Changes in the expression of clock genes have also been reported in the ageing mouse kidney[177,180]. Dysregulation of renal rhythmicity involving changes in the circadian patterns of diuresis-regulating hormones or downstream molecular mediators of renal salt and water transport warrant consideration as potential factors in the aetiology of nocturnal polyuria in healthy ageing adults.

Results from studies including healthy young and old adults have clearly shown that ageing alters the secretory rhythm of hormones that regulate the salt–water balance[181,182]. For example, results from an observational study including old adults (>60 years old) with and without nocturia showed that the circadian rhythm of AVP secretion was attenuated or lost in individuals with nocturia whose diurnal variation in urine output was disrupted[181]. Gender differences in AVP levels during ageing have also been reported in a clinical study, with higher AVP plasma concentration observed in males than in females, suggesting a greater response in AVP and renin–angiotensin system sensitivity in men[183]. The plasma levels of ANP, which could also be implicated in nocturnal polyuria through increasing renal Na^+ excretion, in turn suppressing AVP release, and decreasing RAAS activity[184], have been shown to be higher in old (65–75 years old) than in young (20–25 years old) adults[178]. In the same study, a clear circadian pattern of plasma ANP with an acrophase early in the afternoon was also shown in young but not in older individuals, indicating that the inhibitory action of ANP on the circadian phasic increase in renin, aldosterone and cortisol is lost with ageing[178]. However, in a study including age-matched older men (mean age 62.8–63.3 years old) with nocturnal polyuria, with nocturia not associated with nocturnal polyuria, and without nocturia, no differences in plasma renin and aldosterone levels were shown among the three groups[185]. Results from a study including men ≥60 years old with or without nocturnal polyuria also showed no differences in AVP levels between the two groups[186]. Moreover, the use of desmopressin to treat nocturnal polyuria in older patients showed a limited effect and does not always alleviate the symptoms[187]. These findings indicate that loss or attenuation of circadian rhythms for diuresis-regulating hormones cannot fully explain the nocturnal shift in urine production in healthy older adults, and highlight the contribution of other factors in altering the rhythmicity of water and solute excretion.

Age-related changes in the circadian clock regulation of the kidney transcriptome also contribute to nocturnal polyuria and nocturia. In a study including young (6 months), old (18 months) and aged (27 months) male mice, an age-associated decline in the number of rhythmically expressed genes was shown across various tissues, with the largest change in rhythmically expressed genes observed in the kidney (75% decline from young to old mice)[180]. Notably, ageing was shown to blunt the oscillatory expression patterns of the *Scnn1a* and *Atp1a1* genes, which encode the alpha subunits of ENaC and Na^+-K^+-ATPases, respectively[180]. Loss of the diurnal pattern of expression of these genes affects the renal circadian rhythmicity of Na^+ and K^+ handling, leading to increased nocturnal Na^+ excretion and contributing to nocturnal polyuria[37]. A decline in clock genes *Per1* and *Per2* rhythmicity was also observed in the ageing mouse kidney[177,180]. Thus, age-related decline in renal *PER1* rhythmicity might have a role in driving changes in the diurnal pattern of Na^+ secretion that contributes to nocturnal polyuria, even when aldosterone levels remain unaltered.

Desynchronization of renal rhythmicity might also have a role in nocturnal polyuria in other contexts. For example, in older men (mean age 61.1 years old) with nocturia, decreased day-to-night ratios of diuresis are associated with increased night-time mean arterial pressure, which could be responsible for nocturnal polyuria, as essential hypertension has also been implicated in the pathophysiology of nocturnal polyuria[188–190]. Dysregulation of water and electrolyte excretion rhythms was shown to be closely associated with abnormal blood pressure and a non-dipping pattern (which refers to a loss of nocturnal decrease in blood pressure during sleep) at night-time[191,192]. In one of these studies, the enhanced nocturnal natriuresis and reduced fall in blood pressure in non-dippers were normalized by dietary Na restriction, suggesting the importance of circadian urinary sodium exertion in maintaining variation of blood pressure[191]. In other studies, dietary Na restriction was also shown to reduce nocturnal polyuria in patients with excessive salt intake, as well as in renal allograft recipients, indicating that restoring circadian natriuresis through lifestyle modification could be effective as a behavioural therapy for nocturnal polyuria[193,194]. These findings, combined with the evidence that *Cry*-null mice develop salt-sensitive non-dipper hypertension[161], suggest the involvement of the peripheral circadian clock and a potential role for desynchronization of renal rhythmicity in the pathogenesis of nocturnal polyuria.

Dysregulation of circadian rhythm of the bladder as a potential cause of nocturia

In coordination with the central clock, the bladder expresses its own peripheral clock genes in a circadian fashion, which leads to time-dependent variation in bladder sensation and excitability.

Physiology of diurnal and nocturnal bladder function

Humans have a diurnal variation in the amount of urine volume voided per micturition, which increases at night and often reaches a maximum value during the first urine in the morning[195,196]. Mice and rats also show a diurnal variation in voided volumes, indicating the existence of common underlying mechanisms of this process in mammals[101,102,197–202]. A diurnal rhythm in detrusor smooth muscle responses to stimulation by carbachol was shown in isolated mice bladder samples, with peak contractile activity at 12 h, which correlates with the intrinsic peak level of *Per2*, suggesting that muscarinic-mediated bladder contractility might undergo circadian control[203]. In guinea pigs, diurnal differences were also observed in the effects of stroking and stretch on the activity of bladder low-threshold and high-threshold muscular mucosa and afferent nerves, with a greater response observed during the day than at night[204]. In humans, maximum urine flow rates were shown to be reduced overnight and early in the morning[196,205–207]. Together, these findings suggest that the bladder has a diurnal rhythm that shifts towards storing urine during the inactive (sleep) period and expelling urine during the active (awake) period. Cystometric and flowmetric data including video sequences from implantable telemetric monitors in miniature pigs showed day-to-night differences in urinary frequency, possibly as a result of the circadian rhythmic detrusor contractility and mechanosensory input[208]. However, in organ bath studies using mouse bladder strips, the contractile response to an electrical field stimulation set to directly stimulate the detrusor smooth muscle did not show a circadian pattern in muscle contraction[203,209]. Thus, the diurnal variation in urine flow rates might require intricate coordination between central and peripheral circadian rhythmic mechanisms, rather than depend on the contractile properties of an isolated organ.

Potential molecular mechanisms underlying rhythmic bladder function

Increasing evidence suggests that the peripheral bladder clock is involved in the generation of diurnal rhythmicity of bladder function. Results from early studies showed the circadian rhythmic expression of clock genes in the bladder and led to identification of a group of genes whose expression vary diurnally, introducing the idea of the clock-mediated regulation of genes involved in bladder storage and voiding function[101,210]. Connexin 43 (CX43), a gap junction protein with major roles in intercellular signalling and modulation of bladder hypersensitivity, contributes to the diurnal variation of bladder capacity, and is also transcriptionally regulated by the clock gene *REV-ERBA*[101].

Results from subsequent studies showed that urothelial regulation of bladder function is also influenced by the molecular clock[100,197,211–214] (Fig. 3). In addition to a barrier function, the urothelium has a central role in the mechanisms of bladder sensation and perception of the extent of bladder fullness[215,216]. In mouse bladder mucosa, some molecular mediators of the urothelial response to mechanical stimulation, including the mechano-sensor PIEZO1, the mechano-sensitive transient receptor potential cation channel subfamily V member 4 (TRPV4) receptor, the connexin 26 (CX26) channel and the vesicular nucleotide transporter (VNUT), were shown to undergo diurnal fluctuation[211,213,214]. In primary cultures of mouse urothelial cells, TRPV4 and PIEZO1 were also shown to be involved in the circadian rhythm of stretch-induced changes in intracellular Ca^{2+} concentration[212].

The urothelium responds to bladder distension by releasing important urothelial mechanotransmitters, including ATP[215,216]. Growing evidence suggests a circadian rhythmic pattern of purinergic signalling, which might contribute to periodic changes in bladder excitability[217]. Within the bladder, ATP release into the lumen has a diurnal pattern, and urothelial CX43 has been shown to have a role in this pattern, possibly through forming hemichannels to enable cellular ATP efflux[100]. Systemic *Cx43* heterozygous mice showed larger functional bladder capacity than wild-type mice both in active and inactive phases as measured through the automated voided stain-on-paper technique[101]. Mice with a urothelium-specific Cx43 deletion showed a larger bladder capacity than wild-type mice, with less luminal ATP release in response to bladder distension only during the active phase[197]. The expression of CX43 in the urothelium follows a circadian rhythm and peaks during the active phase[100,197]. Thus, these findings suggest that CX43 in the urothelium has a role in the perception and regulation of responses to bladder distension in the active phase, possibly through altering the number of CX43 hemichannels that mediate ATP release[100].

Understanding how the peripheral clock of the bladder is tuned independently from CNS regulation is an important issue[218]. The major entrainers of the peripheral clock vary in different organs and tissues; for example, in the liver, major entrainers of functional rhythm are dietary factors, as evidenced by data showing that restricted feeding can rapidly shift the liver's rhythm by 10 h, with the presence of an intact central clock[219]. Mechanisms underlying synchronization of the peripheral clock involve hormones such as glucagon and growth factors such as IGF1, which are responsive to dietary intake and help to synchronize the liver's clock to metabolic signals, overriding cues from the central clock[220]. In the bladder, local activation of muscarinic and purinergic receptors was shown to influence the peripheral bladder clock by shifting peak expression of *PER2* to an earlier time, indicating that local receptors could regulate bladder rhythms[203]. Glucocorticoids have been identified as synchronizing agents of the bladder clock[221]. In immortalized human urothelial cells, glucocorticoids were shown to modulate the circadian expression of *BMAL1* in a concentration-dependent and time-dependent manner[221]. In adrenalectomized mice, treatment with corticosterone in the early sleep period, which is the opposite phase of corticosterone physiological peak, resulted in an 8–12-h shift in the expression of the major clock genes and a loss of diurnal rhythm of volume voided per micturition[221]. In a study in mice, peripheral clocks were also shown to function in the urethral sphincter and in the L4/L5 spinal cord, whereas no rhythm of clock gene expression in the periaqueductal grey matter and pontine micturition centre was reported[222]. Results from these studies suggest that excitatory receptors, neurotransmitters and hormones could regulate the rhythmic pattern of peripheral clock genes. The diurnal variation in the micturition pathway might also be related to diurnal differential regulation of bladder function. Studying this regulatory mechanism is a topic for future research.

The role of disrupted rhythmic bladder function in nocturia

In mice with disrupted biological clocks, such as *Cry*-null and *Clock* mutant mice, no circadian rhythms were observed in urine volume voided per micturition, indicating that bladder function is influenced by the circadian clock[101,223]. Under normal physiological conditions, diurnal rhythms generated by the circadian clock system gradually decline in function with ageing[224]. In mice, a decrease in *Per2* expression in the bladder and loss of normal *Per2* response to local activation of muscarinic and purinergic receptors was observed with ageing[203]. In a study including patients with or without OAB symptoms, higher urinary ATP concentration was observed in patients with OAB than in patients without OAB and the ratio of ATP-to-creatine correlated positively with age[225]. These results could explain the evidence that both prevalence of

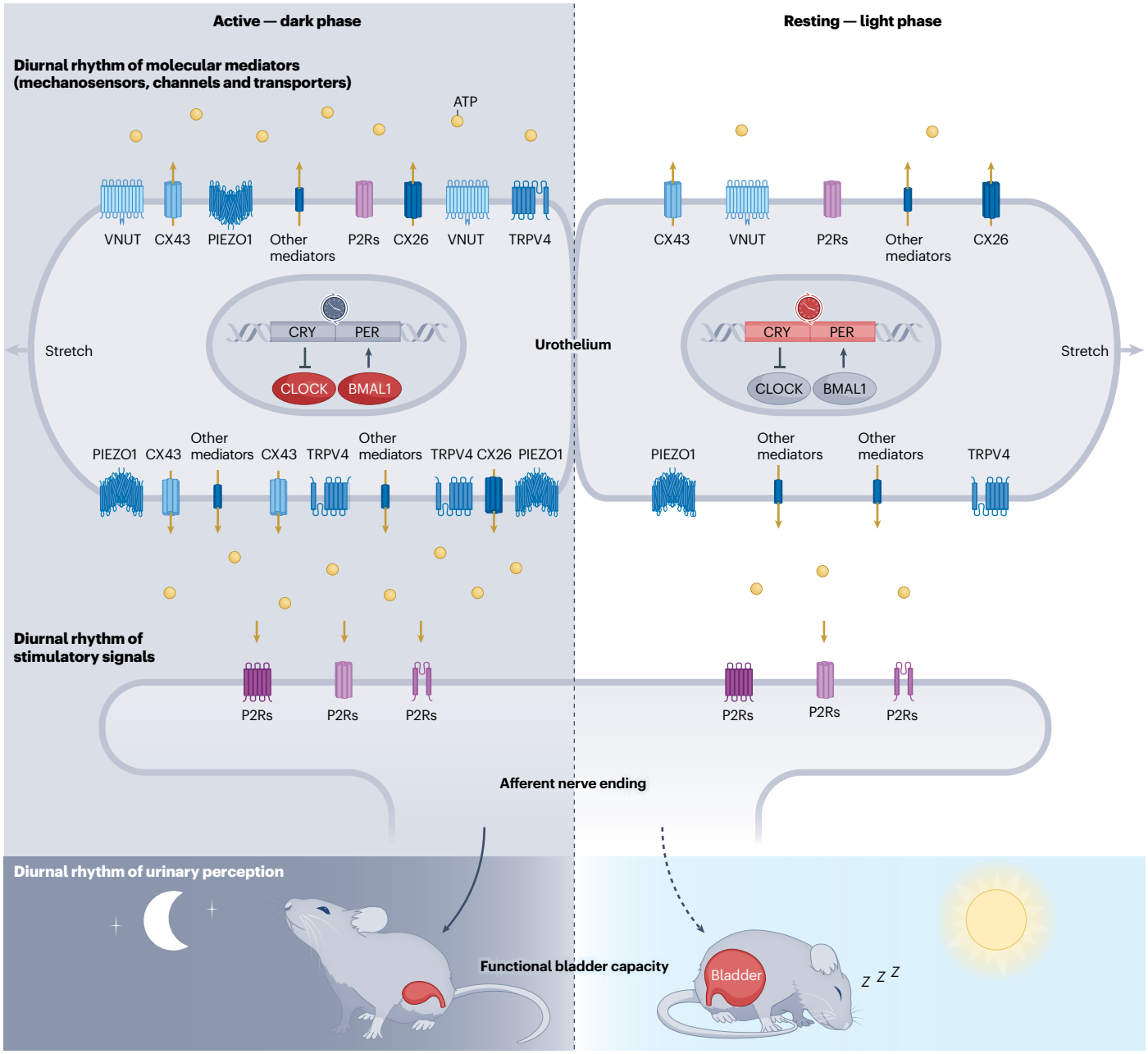


Fig. 3 | Circadian modulation of urothelial receptors and signals in regulation of diurnal rhythmic bladder function. Putative role of the urothelium in the physiological diurnal rhythm of bladder capacity. The circadian modulation of bladder function by the peripheral bladder clock is shown. The diurnal rhythm of molecular mediators, including connexin 43 (CX43), CX26, vesicular nucleotide transporter (VNUT), and mechanosensors such as PIEZO1 and transient receptor potential cation channel subfamily V member 4 (TRPV4), regulates ATP release in response to bladder distension, influencing urinary sensation and bladder capacity. During the active (dark) phase, the expression of CX43, CX26 and VNUT peaks, facilitating increased ATP release through the hemichannels formed by CX43 and CX26. This process leads to increased bladder sensitivity and modulation of bladder capacity. The mechanosensors PIEZO1 and TRPV4 also show diurnal fluctuations, contributing to the circadian control of ATP release. Released ATP activates P2 receptors on afferent nerves, mediating the bladder's sensory response to distension. In the resting (light) phase, the expression of these mediators decreases, resulting in reduced ATP release and reduced bladder excitability, supporting time-dependent regulation of bladder function in alignment with the circadian cycle. BMAL1, brain and muscle aryl hydrocarbon receptor nuclear translocator-like protein 1; CLOCK, circadian locomotor output cycles kaput; CRY, cryptochrome; PER, period; P2Rs, purinergic type 2 receptors. Adapted from ref. 197, CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/).

OAB and severity of nocturnal frequency increase with age[226–228], suggesting that these phenomena could be possibly ascribable to the loss of clock gene expression rhythmicity and the disruption of the diurnal variation of mechanosensory receptors.

A relationship between disruption of the bladder clock and diurnal rhythmicity of bladder function has also been reported in pathological mouse and rat models[200–202,229]. Restraint-stressed mice and spontaneously hypertensive rats showed altered rhythms of TRPV4, PIEZO1 and CX26 expression in the bladder, which were accompanied by a decrease or loss of diurnal variations of bladder capacity, indicating that systematic disorders might affect voiding behaviour by influencing gene expression rhythms within the bladder[200–202]. In Dahl salt-sensitive rats, salt loading resulted in altered expressions of clock genes in the bladder and increased bladder capacity, which were partially restored when salt intake was reduced, indicating a close relationship between lifestyle, peripheral clock and circadian voiding pattern[229]. Thus, increasing evidence suggest a role for the bladder clock in generation of a diurnal rhythm of bladder capacity, and a potential relationship between disruption of clock-regulated bladder capacity and nocturia. As knowledge in this area increases, major advances are expected in the development of novel chronotherapies for nocturia.

Future research on chronotherapies

The disruption of one or more components within the brain–kidney–bladder circadian axis has an essential role in the onset of nocturia. Thus, understanding the interrelated molecular basis of circadian regulation and dysregulation is imperative so that strategies for prevention, management and treatment of nocturia based on chronobiology can be developed.

Chronotherapies based on environmental and behavioural changes

Some environmental and lifestyle modifications are known to alter circadian timing, contributing to a variety of health conditions[230,231]. For example, the master clock is mostly regulated by ambient light perceived by the retina[232]; thus, non-invasive light therapy might be effective in maintaining and resynchronizing circadian rhythmicity[232,233]. This hypothesis is supported by clinical evidence showing that timed light exposure for critically ill patients in intensive care units normalized the circadian phase of physiological behaviour (as determined by the urinary 6-sulfatoxymelatonin rhythm), as well as preventing and shortening postoperative delirium episodes[234–237]. The feeding–fasting cycle in humans also follows a natural circadian pattern, and irregular feeding behaviour can reset many circadian clocks in peripheral endocrine glands and metabolic organs, exerting deleterious effects on metabolic health and energy homeostasis[238]. Consequently, in men with prediabetes (with both elevated HbA1c levels and impaired glucose tolerance), time-restricted feeding (consisting of a limited food access period during the active phase) was shown to be effective in treating type II diabetes through improving insulin sensitivity and β cell responsiveness[239], and also in preventing other metabolic disorders, such as obesity, cardiovascular events, hepatic steatosis, and hypercholesterolaemia[240]. Moreover, in older adults with chronic insomnia, scheduled behavioural activity (such as aerobic physical exercise) was shown to regulate rhythms and cause phase shifts, in turn improving sleep quality, mood and quality of life[241–244].

Lifestyle interventions are considered to be the first-line approach in the management of nocturia. These modifications include limiting drinking before sleep, encouraging physical exercise and restricting salt intake. Further evidence is needed to confirm the relevance of timed fluid consumption, timed physical activity and timed sleep–waking patterns in relieving nocturia and modifying circadian control mechanisms.

Chronotherapies to optimize drug efficacy

A high number of drug targets and metabolizing enzymes are expressed in a circadian fashion; thus, chronotherapy approaches can be used to optimize drug efficacy[59,230,231,245,246]. The absorption, distribution, metabolism and elimination of drugs are largely affected by rhythmic changes in liver metabolism and renal glomerular filtration that are regulated by clock genes[246]. Thus, circadian-controlled delivery of therapeutics might be developed according to the biological rhythms of different conditions to achieve maximal efficacy and minimal adverse effects. For example, timed melatonin therapy has been proposed to rectify the circadian misalignment owing to jet lag and shiftwork, as melatonin given in the late biological afternoon or early biological morning (over a 24-h cycle) resulted in advanced and delayed circadian rhythms, respectively[247]. The hepatotoxicity of cyclophosphamide, a medication used as chemotherapy for cancer and autoimmune diseases, is also time dependent, and is attributed to diurnal oscillations of the expression and metabolism of cyclophosphamide-metabolizing enzymes (such as CYP2B10), which have been shown to be controlled by *CLOCK*[248]. Myeloid cells were shown to adhere to atherosclerotic lesions in a circadian fashion, and timed pharmacological neutralization of the CCL2–CCR2 axis (a signalling pathway that triggers chemokine adhesion and immobilization on arterial vessels) during the peak of arterial myeloid cell recruitment inhibits atherosclerosis without disturbing microvascular recruitment[249]. Similarly, chronotherapeutic schedules of several anticancer agents have shown benefit in improving tolerability and reducing cytotoxicity towards healthy cells without jeopardizing tumour control[250].

Considering the role of central and peripheral circadian rhythm disruption in the pathogenesis of nocturia, chronotherapeutic approaches can be established in the future. Future research should focus on developing novel medications and modulating their pharmacokinetics to reach peak plasma concentration during the main sleep period to reduce urine production and increase bladder storage functional capacity during sleep.

Chronotherapies targeting manipulation of the central oscillators

Direct manipulation of the TTFL using small-molecule modulators is an intriguing approach to regulating central oscillators. For example, stabilizing *CRY* expression could lengthen the period and reduce the amplitude of circadian oscillators. Treatment with central circadian clock modulators, such as KL001, SHP656, KL101, TH301 and KS15, was shown to improve glucose tolerance in patients with diabetes[251], as well as enhancing brown adipocyte differentiation in vitro[252] and inhibiting cell proliferation of glioblastoma stem cells and breast cancer cells, indicating the potential of these therapies in future clinical applications[253,254]. Moreover, chemicals that modulate the secondary feedback loop in the clock cycle have also been shown to potentiate circadian wheel running activity and clock gene oscillation and, therefore, might restore metabolic homeostasis in several behavioural and metabolic diseases[231]. For example, selective agonists of REV-ERB (SR0990 and SR9011) have been shown to restore glucose metabolism, reduce diet-induced obesity and ameliorate anxiety by altering circadian behaviour and targeting core clock gene (*BMAL1*, *PER1* and *PER2*)

expression in the hypothalamus of mice, suggesting a promising role for REV-ERB agonists in resynchronizing rhythms of behaviour and metabolic processes[255,256]. Additionally, nobiletin, a direct ROR agonist, improves metabolic homeostasis and protects against inflammation and atherosclerosis by enhancing the amplitude and lengthening the period of circadian rhythms, as evidenced by the remodelling of clock gene expression observed in both PER2::Luc reporter cells and transgenic mice receiving nobiletin treatment[257–259].

In summary, small-molecule modulators targeting central and peripheral clock genes might have great potential in reversing metabolic, behavioural and attentional disorders, although the safety and effectiveness of these agents still remain to be explored in clinical trials.

Future perspectives of chronotherapies in nocturia

To date, none of the available regulators of clock oscillators, behavioural chronotherapies or circadian-controlled dosing modalities has been shown to have a clear effect in the treatment of nocturia. In a restraint-stress mouse model, the disrupted circadian voiding pattern accompanied by clock gene abnormalities could be reversed through oral administration of PF670462, an inhibitor of the enzyme responsible for PER phosphorylation, indicating that the modulation of clock genes could be a potential therapeutic approach to nocturia[201]. In a subsequent study from the same group, the inhibitory effects of GsMTx4, a PIEZO1 inhibitor, were shown to change in a circadian rhythmic fashion[260]. In mice, both a low dose (0.75 mg/kg) of GsMTx4 given during the nadir expression of PIEZO1 and a high dose (1.5 mg/kg) of GsMTx4 given during the zenith expression of PIEZO1 significantly ($P < 0.01$) reduced voiding frequency, suggesting that the time of medication might affect the therapeutic effect[260]. In a study in which metabolomic analysis was carried out on urine samples from men aged 65–80 years, increased urinary serotonin and decreased levels of 3-hydroxypropionic acid (a metabolite of β-alanine metabolism involved in psychological disorders) and 3-indoleacetonitrile (a metabolite of tryptophan metabolism involved in metabolic syndrome pathogenesis) were shown to be highly associated with nocturia, suggesting redressing the circadian regulation of these metabolic pathways as a potential treatment for nocturia[261]. Additional evidence from studies in mice showed that serum fatty acid metabolites fluctuate with circadian rhythm in wild-type mice, but the fluctuations are absent in mice with a *Clock* gene mutation[262]. Specifically, the loss of regular circadian rhythm regulation of fatty acid metabolism led to increased serum levels of palmitoylethanolamide, which activates the pontine micturition centre and induces nocturia by activating G protein-coupled receptor 55 in the urothelium[263]. Together, these results suggest that regulators of fatty acid metabolic rhythms during the sleep phase might be a potential chronotherapy for nocturia. From a clinical perspective, initial results from a 2023 clinical trial including patients with nocturia ≥50 years old showed that treatment with a mixture of nobiletin and tangeretin extracted from *Citrus depressa* peels significantly reduced night-time voiding frequency (0.5 times, $P = 0.04$) compared with placebo[264]. However, no significant improvement was shown in nocturnal bladder capacity and nocturnal polyuria index ($P = 0.61$ and $P = 0.3$, respectively). In another pilot study to investigate the effect of hormonal therapy on voiding patterns and renal circadian rhythms in postmenopausal women, oestrogen treatment for 3 months did not significantly change nocturnal parameters calculated from a frequency-volume chart ($P = 0.056$ for number of nocturnal voids; $P = 0.6$ for mean nocturnal voided volume; $P = 0.2$ for nocturnal urine volume), although the same hormonal treatment restored circadian rhythm of free water clearance (increased during daytime and decreased during night-time) in postmenopausal women with nocturnal polyuria[265]. Considering the ambiguous results from existing studies, future studies are needed to define the most appropriate circadian medications, treatment dosage and delivery modality for treating nocturia.

Conclusions

Coordination of the brain–kidney–bladder circadian axis is essential for normal lower urinary tract function, and disruptions of this axis can result in nocturia. Increasing evidence shows the existence of common mechanisms among clock gene regulation, sleep behaviour, urine production and voiding patterns, highlighting the potential benefits of chronotherapies for nocturia. However, many questions remain unsolved. For example, the feasibility of using circadian behaviour therapy — including timed feeding, sleeping and light exposure — to reduce nocturia should be investigated. Additionally, whether modulators of clock genes could be safely used to manipulate bladder sensitivity and capacity individually for each patient remains to be assessed. Last, the interrelated connections among bladder clock genes, rhythmic expression of neurotransmitters and diurnal bladder function need to be identified. Understanding the crosstalk among components within the brain–kidney–bladder circadian axis will be invaluable in discovering safe, effective and cost-efficient therapeutics to resynchronize the clock for patients with nocturia.

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Author contributions

Q.-X.S., S.O.S., H.N., H.-H.J. and R.J. researched data for the article. All authors contributed substantially to discussion of the content. All authors wrote the article. All authors reviewed and/or edited the manuscript before submission.

Competing interests

The authors declare no competing interests.

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