Title: Role of circadian rhythms and melatonin in bladder function in heath and diseases

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Abstract

The circadian system modulates all visceral organ physiological processes including urine storage and voiding. The “master clock” of the circadian system lies within suprachiasmatic nucleus of the hypothalamus while “peripheral clocks” are found in most peripheral tissue and organs, including the urinary bladder. Disruptions of circadian rhythms can cause organ malfunction and disorder or exacerbate pre-existing ones. It has been suggested that nocturia, which develops mostly in the elderly, could be a circadian-related disorder of the bladder. In the bladder, many types of gap junctions and ion channels in the detrusor, urothelium and sensory nerves are likely under strict local peripheral circadian control. The pineal hormone, melatonin, is a circadian rhythm synchroniser capable of controlling a variety of physiological processes in the body. Melatonin predominantly acts via the melatonin 1 and melatonin 2 G-protein coupled receptors expressed in the central nervous system, and many peripheral organs and tissues. Melatonin could be beneficial in the treatment of nocturia and other common bladder disorders. The ameliorating action of melatonin on bladder function is likely due to multiple mechanisms which include central effects on voiding and peripheral effects on the detrusor and bladder afferents. More studies are warranted to determine the precise mechanisms of circadian rhythm coordination of the bladder function and melatonin influences on the bladder in health and diseases.

1. Introduction

The circadian system powerfully modulates 24hr rhythms of all visceral organ physiological processes, optimising efficiency and coordinating their functions. The "master clock" of the circadian systems lies within the suprachiasmatic nucleus (SCN) of the hypothalamus (Ralph et al., 1990; Hastings et al., 2018). In mammals, melanopsin-expressing photoreceptors in the retina detect changes in light condition and signal to the SCN neurons leading to Ca^{2+} influx via glutamate receptor activation. This, in turn, increases the expression of *Clock* and *Bmal1* genes. *Clock* and *Bmal1* protein dimerise and induce the expression of *Per1/2, Cry1/2, Rorα, and Rev-erb,* each of which can cyclically influence the expression of other non-circadian system genes (Reppert and Weaver, 2002; Duffy and Czeisler, 2009; Okamura et al., 2010; Xie et al., 2019). A positive feedback loop is formed by *Rev-erb* which increases *Bmal1* expression, and a negative feedback loop is formed by *Per1/2* and *Cry1/2* which dimerise and inhibit *Clock/Bmal1*. These feedback loops in the SCN form a ~24hr oscillation cycle in mammals and can influence the circadian rhythms found in most peripheral tissues and organs (termed "peripheral clocks") such as the gut, liver, adipose tissue, immune cells and skeletal muscle (Reinke and Asher, 2016; Hastings et al., 2018). The SCN master clock aligns, tunes, and prevents the dampening of these peripheral clocks via neural signalling through sympathetic and parasympathetic nerves, hormonal signals from pineal and adrenal glands, and indirectly via behavioural control such as sleep-wake cycles and feeding (Ohdo 2010; Richards and Gumz, 2012). While the central SCN clock influences peripheral clocks in many parts of the body, some peripheral organs and tissue such as the gut and liver have circadian rhythm of clock genes acting independently of the SCN (Ferrell and Chiang, 2015; Koronowski et al. 2019). Peripheral clocks also exist in the urinary bladder which depends on recently discovered circadian clock oscillation genes in the bladder wall (Negoro et al., 2012; Noh et al., 2014; Ihara et al., 2017; Ali et al., 2020; Ihara et al., 2021) and dorsal root ganglia (DRG) neurons (Zhang et al., 2012).

Circadian rhythms modulate urinary voiding in mammals, including humans, with increased occurrence during active phases and decreased occurrence during inactive phases (Kirkland, Lye et al. 1983; Herrera and Meredith, 2010; Noh et al., 2011; Negoro et al., 2012). Urinary voiding peaks during the early morning, with a consistent pattern throughout the day and little to no occurrence at night (Noh et al., 2011). Many parameters of voiding in both humans and

animals such as urine volume, voiding frequency, voiding volume per void and electrolyte excretion have significant circadian rhythm variation (Minors and Waterhouse 1982; van Haarst et al., 2004; Parsons, 2007, Van Hoeck et al. 2007; Noh et al., 2011).

Disruptions to normal circadian rhythms can significantly impact sleep and quality of life (Vetter, 2020), with recent research turning towards melatonin as a potential treatment option of human disorders that may be caused by circadian disruption. The hormone melatonin (N-acetyl-5-methoxytryptamine) is involved in the synchronisation of the peripheral clocks by the central clock and serves as feedback mechanisms for SCN neurons (Pandi-Perumal et al., 2008; Prasai et al., 2011). It is produced and released primarily during darkness by pinealocytes of the pineal gland. The timing of melatonin secretion by the pineal gland is associated with the timing of sleep propensity and coincides with decrease in core body temperature, performance, and alertness (Claustrat et al., 2005; Arendt 2006). Melatonin is considered a powerful regulator of circadian rhythms with concentrations in the blood and urine peaking during the night, stabilising the sleep-wake cycle (Reiter et al., 2009). However, many cells in other organs and tissues can synthetise melatonin locally. These include the retina, liver, gut, kidney, skin, and immune cells (Tan et al., 1999; Acuna-Castroviejo et al., 2014; Reiter et al., 2014; Labrecque and Cermakian, 2015; Gonzalez-Arto et al., 2016; Slominski et al., 2018). Therefore, in addition to its hormonal role, melatonin is considered also as an important paracrine tissue mediator.

Two types of G-protein coupled receptors, melatonin 1 (MT1) receptor and MT2 receptor, have been identified in the CNS and in peripheral tissues such as blood vessels, heart, lung, gut, live, kidney, and bladder (Dubocovich and Markowska 2005; Pandi-Perumal et al. 2008; Hardeland et al., 2011). In the SCN, melatonin acts via MT1 receptors to reduce neuronal activity, and via MT2 receptors to cause a circadian phase shift (Dubocovich, 2007). Some of the action of melatonin is due to its effects on nuclear receptors of the ROR family or directly on intracellular enzymes and Ca^{2+} binding proteins since melatonin is membrane permeable (Dubocovich and Markowska 2005; Hardeland et al., 2011; Emet et al., 2016). Melatonin receptors may play a role in the regulation of various physiological processes and therefore are important in many disorders including circadian rhythm sleep disorders, neurogenerative brain disorders and some cancers (Macchi and Bruce 2004; Pandi-Perumal et al. 2008; Talib et al., 2021). It has been recently suggested that abnormalities in clock genes in the bladder and impaired melatonin production in

elderly could be one of the causes of the nocturia (Sugaya et al. 2007; Noh et al., 2011; Negoro, et al., 2012; Negoro et al. 2013; Noh et al., 2014, Obayashi et al., 2014; Ihara et al., 2017; Ihara et al., 2021). Melatonin can regulate bladder function via central CNS effects and/or local effects on the detrusor and sensory neurons innervating the bladder (Gomez-Pinilla et al., 2008; Matsuta et al., 2010; Han et al. 2012; Ramsay and Zagorodnyuk, 2022). The review summarises the role of the circadian system in the bladder, and the influence of melatonin on bladder function in health and diseases.

2. Circadian rhythms of the bladder and role of melatonin

2.1 Clock genes and bladder voiding

Clock mRNA does not exhibit a circadian rhythm in either mouse or rat bladder urothelium, but its deletion is widely used as an animal model for circadian disruption, and these models do exhibit changes in rhythms of voiding (Ihara et al., 2017; Kimura et al., 2019). Bladder *Clock* protein is yet to be investigated; therefore, it is possible that post-translational *Clock* protein does demonstrate a rhythm. Interestingly, *Clock* knockout mice are used as animal model of nocturia, since during the inactive phase these mice showed greater urine volume accompanied by increased voiding frequencies and smaller urine volume per void compared to wild-type mice (Ihara et al., 2017).

The mRNA of other oscillating clock genes does exhibit rhythmic profiles; however, the timing of their peaks and nadirs are not always consistent between studies. For example, there is a consensus that *Bmal1* mRNA in the urothelium peaks during active phases and nadirs during rest phases in mice and rats. However, for *Per1/2* mRNA, a species difference exists with peaks during the rest phase for mice (Negoro et al., 2012; Noh et al., 2014; Ihara et al., 2017, Ihara et al., 2019) and peaks during the active phase for rats (Kimura, Honda et al. 2019). Interestingly, an *ex vivo* study demonstrated that bioluminescence of *Per2* protein peaked in the early active phase while *in vivo* studies showed that it peaked in the middle of the active phase (Ihara et al., 2019). This suggests that *Per2* mRNA and protein rhythms are not only species dependent, but also different between *in vivo* or *ex vivo* conditions. Nonetheless, a study has shown that *Per2* genetic knockout mice show loss of rhythms in water intake and urine voiding. Whether the loss of rhythm in voiding

is due to the loss of rhythm in water intake is not clear (Noh et al., 2014). Intermittent stress in mice causes a loss of *Per2* rhythms in the bladder and subsequent loss in rhythms of voiding frequency and voiding volume without disruptions to water intake rhythms (Ihara et al., 2019). This suggests that perhaps that *Per2* is a strong driver of voiding patterns and warrants further research into the influence of water intake on voiding patterns.

The other clock genes, e.g., *Cry1/2*, *RORα*, and *Reverb*, are less studied. *Cry1/2* mRNA peaks during the inactive phase in mouse bladder (Ihara et al., 2017) and genetic knockout causes a complete loss of voiding rhythms (Negoro et al., 2012). However, *Cry1/2* mRNA does not show any rhythm in rat bladder (Kimura et al., 2019), likely a species difference. The mRNA profile of *Rev-erb* is consistent between mouse and rat with peaks during the inactive phase and nadirs during the active phase (Noh et al., 2014; Ihara et al. 2017; Ihara et al., 2019; Kimura et al., 2019). Lastly, and perhaps the least studied, *RORα* peaks during the active phase and nadirs during the inactive phase (Ihara et al., 2017).

2.2 Circadian rhythms of connexins and ion channels in the bladder

The clock system regulates the rhythmic expression of various connexins and ion channels within the bladder detrusor and urothelium. Connexins form gap junctions between smooth muscle cells, interstitial cells, and urothelial cells; they regulate the communication between coupled cells via the transmission of ions and other intercellular messengers. The detrusor consists of separate smooth muscle bundles. Smooth muscle cells within the bundles are connected predominantly via connexin 45 (Cx45)-derived gap junctions (Sui et al., 2003), with significantly less Cx43 detected in normal detrusor (Christ et al., 2003; Neuhaus et al., 2005). In contrast, interstitial cells, which lie in between the muscle bundles, are predominantly interconnected via Cx43-derived gap junctions (van der Roskams et al., 2004), similar to those located in the suburothelial interstitial cell network (Sui et al., 2002). It has been suggested that upregulation of Cx43 in the detrusor may be responsible for the storage symptoms of overactive bladder and interstitial cystitis. Significant upregulation of Cx43 in the detrusor has been demonstrated in patients with urgency symptoms (Neuhaus, Pfeiffer et al. 2005), in the obstruction-induced bladder overactivity in rats (Christ et al., 2003) and cyclophosphamide-induced cystitis in mice (Okinami et al., 2014). Cx43 also

involved in the communication between urothelial cells, although the predominant type of connexin-derived gap junctions between urothelial cells is Cx26 (Ikeda et al., 2007).

Two specific connexins have been studied in the bladder urothelium, connexin 26 (Cx26) and connexin 43 (Cx43) in relation to circadian rhythms. Both Cx26 and Cx43 mRNA peak in the active phase and nadir in the inactive phase of mice (Negoro et al., 2012; Ihara et al. 2017; Ihara et al., 2018). Rhythms of Cx26 are lost in *Clock* mutants (Ihara et al., 2017; Ihara et al., 2018), whilst rhythms of Cx43 are lost in *Cry1/2* mutants (Negoro et al., 2012), suggesting that different components of the clock system regulate different connexins.

There are several types of mechanosensitive cells in the bladder including urothelial cells, interstitial cells, smooth muscle cells, and mechanosensitive endings of spinal afferent nerves that innervate the bladder (Wellner and Isenberg 1993; Hashitani et al., 2004; Zagorodnyuk et al. 2009; Lee et al., 2017; Dalghi et al., 2021). The major primary sensors involved in bladder reflexes and mechanosensation from the bladder are urothelial cells and spinal afferent endings within the bladder wall (Zagorodnyuk et al., 2006; Zagorodnyuk et al., 2009; Birder and Andersson, 2013; Marshall et al., 2020; Dalghi et al., 2021). Mechanosensitive non-selective cation channels of the transient receptor potential (TRP) family, TRP vanilloid (TRPV1) and TRPV4, and Piezo1 and Piezo2, within the urothelial cells regulate Ca^{2+} influx and release of ATP and other neuromodulators during bladder distention (Ferguson et al., 1997; Wang et al., 2005; Mochizuki et al., 2009; Miyamoto et al., 2014; Merrill et al., 2016; Girard et al. 2019; Marshall et al., 2020). A current working hypothesis suggests that urothelium-released ATP is crucial for promoting voiding during bladder distension by activating afferent fibres within the bladder wall (Burnstock, 2001; Vlaskovska et al., 2001; Birder and Andersson, 2013; Merrill et al., 2016). It has been demonstrated that extracellular ATP can increase excitability and/or evoke firing of sensory fibres for those classes of bladder afferents that have their receptive fields in the vicinity to the urothelium (Vlaskovska et al., 2001; Zagorodnyuk et al., 2009).

Three circadian-regulated mechano-sensitive ion channels, Piezo1, TRPV1, and TRPV4, have been studied in detail within the bladder mucosa. The mRNA of each of these ion channels peaks during the active phase and nadirs during the inactive phase of mice and rats (Ihara et al., 2018; Kimura et al., 2019; Ihara et al., 2021). Circadian rhythms of Piezo1 and TRPV4 are lost in *Clock* mutant mice (Ihara et al., 2018; Ihara et al., 2021). As have been mentioned previously,

these ion channels in the urothelium influence Ca^{2+} influx and ATP release from urothelial cells which can further influence signalling within the bladder wall. Ca^{2+} influx and ATP release do not exhibit rhythms in quiescent urothelial cells, however, upon stretch there is a higher urothelial cell ATP release (Ihara et al. 2018a, 2018b) and Ca^{2+} influx (Ihara et al., 2018a, 2018b) during the active phase compared to the inactive phase in mice. Rhythmic ATP release was abolished in *Clock* knockout mice and in Cx43 knockout mice (Kono et al., 2021), but not affected by vesicular nucleotide transporter blockade (VNUT; involved in ATP storage) (Ihara et al. 2018a, 2018b). Rhythms of Ca^{2+} influx were lost when Piezo1 and TRPV4 were blocked with their antagonists (Ihara et al., 2017). Interestingly, antagonism of Piezo1 with GsMTx4 (non-selective Piezo1 and Piezo2 antagonist) demonstrated dose and time-of-day dependent effects. For example, when administered during the inactive phase of mice, both low and high doses of GsMTx4 reduced voiding frequency and increased voiding volume. However, when administered during the active phase of mice, this effect was only seen at high doses of GsMTx4 (Ihara et al., 2021). This suggests that time and dose need to be concurrently considered for maximum effectiveness of pharmaceutical interventions, which potentially opens a whole new avenue when treating common bladder disorders.

Functional Piezo1 channels are expressed in all urothelial cell layers while Piezo2 is only expressed in a small subset of superficial umbrella cells. By using conditional urothelial Piezo1 knockouts, it has been recently determined that mechanically induced changes in $[Ca^{2+}]_i$, ATP release and voiding function were unaffected in Piezo1-KO female mice. Interestingly, in male Piezo1-KO mice, there was significant increase in voiding during inactive light phase compared to controls. In conditional urothelial Piezo2-KO male mice, there was significant reduction in voiding volume of the primary void spots found only during the active phase (these are due to micturition events as determined by void spot assays in freely moving conscious mice). In contrast to Piezo1 or Piezo2-KO mice, which have a relatively limited phenotype, dual Piezo1/2 conditional urothelial knockout had the most affected phenotype (Dalghi et al., 2021). Both sexes of these mice had significant decreased $[Ca^{2+}]_i$ urothelial response to mechanical stimulation and almost complete loss of serosal ATP release. However, primary void spots were not affected. This data argues strongly against urothelial released ATP as being essential for normal voiding. There were also other sex-dependent and time of day differences between Piezo2 and Piezo1/2 channel-driven mechanotransduction and voiding function (Dalghi et al., 2021). It is worth mentioning that

stretch-induced firing of low threshold bladder afferents during the distension of the bladder does not require ATP released from urothelium and it is likely due to activation of mechanosensitive ion channels present on peripheral spinal afferent endings (Zagorodnyuk et al., 2006; Zagorodnyuk et al., 2007; Zagorodnyuk et al., 2009; Coste et al., 2010; La et al., 2011; Marshall et al., 2020).

2.3 Circadian rhythms and spinal sensory neurons innervating the bladder

Primary sensory neurons innervating the bladder and their function have been reviewed elsewhere (Zagorodnyuk et al. 2010; Grundy et al., 2019; Christie et al., 2021). Briefly, bladder afferents play a key role mediating both storage and micturition. They are also responsible for all bladder sensations, ranging from physiological sensation of filling and fullness through to lower urinary tract (LUT) symptoms such as excessive urgency, discomfort and pain. Currently, there are 5 different types of bladder afferents described: mucosal (urothelial), muscular, muscular-mucosal (muscular-urothelial), vascular (serosal), and silent. Stretch-sensitive muscular and muscular-mucosal afferent types can be divided further into low- and high-thresholds classes of bladder afferents (Zagorodnyuk et al., 2010; Christie et al., 2021). Bladder innervating primary sensory neuron cell bodies are found in L5 to S4 DRG and to lesser extent from T12 to L3 DRG (Nandigama et al., 2010; Christie et al., 2021).

To date, there has been little attention towards the circadian rhythms of bladder afferents. Our recent study indicated a potential circadian rhythm of at least 3 classes of bladder afferents, mucosal, and low and high threshold muscular-mucosal afferents. All of these afferents demonstrated an increased sensitivity to mechanical stimuli (stroking or stretch) during the day and decreased sensitivity during the night in guinea pigs (Christie and Zagorodnyuk, 2021). Although only measured at 2 opposing time points, this is a strong indicator of a full 24hr rhythm of bladder afferents sensitivity. The mechanisms behind this potential rhythm are unknown.

The endogenous TRPV1 agonist, N-oleoyl dopamine (OLDA), demonstrated a greater direct excitatory effects and potentiation of mucosal afferent responses to mechanical stimuli during the day compared to the night (Christie and Zagorodnyuk, 2021). This raises possibility that mechanosensitive channels found in DRG neurons (TRPV1, TRPA1, and Piezo2) (Coste et al., 2010; La et al., 2011; Marshall et al., 2020) are under peripheral circadian rhythms regulation

similar to the urothelium (Ihara et al., 2018a, 2018b; Kimura et al., 2019; Ihara et al., 2021). TRPV1 is well-known to be involved in nociception in the bladder (Dinis et al., 2004; Charrua et al., 2009; Guo et al., 2013; Jardin et al., 2017) and, therefore, circadian changes in its responsiveness to endogenous agonists (such as anandamide and OLDA) may influence circadian changes in sensations such as discomfort or pain. Intensity of pain sensation is under circadian rhythm control in humans; however, these rhythms vary dependent upon the type of pain. For example, in humans, neuropathic pain tends to peak during the evening whilst headache-related pain tends to peak early morning (2am) (Burish et al., 2019). Bladder distension evokes brainstem-mediated visceromotor responses (VMRs), produced by abdominal muscle contractions, that can be assessed by recording their electromyographic activity (Ness and Gebhart, 1990; Ness and Elhefni, 2004; Zagorodnyuk et al., 2011). VMRs induced by noxious intravesical pressures (40-60 mmHg) have been established as surrogate marker for bladder pain (Ness and Gebhart, 1990; Ness and Elhefni, 2004; Sadler et al., 2014). So far, there is no data available whether there is a circadian rhythm in bladder-related pain responses and behaviours. In the gut, there is a conflicting data whether VMRs evoked by colorectal distension in rats exhibits a circadian rhythm (Gschossmann et al., 2001; Botschuijver et al., 2016).

The summary of the mechanisms underlying circadian system regulation of the bladder function is illustrated in Fig. 1.

In the gut, mechanosensitive gastric vagal afferents are under powerful circadian control and therefore their responses to food-related stimuli fluctuate significantly depending on the time of day (Page, 2021). Primary spinal sensory neurons innervating the large intestine have been reviewed extensively elsewhere (Brierley et al., 2018), however, to date, there are no studies investigating the circadian rhythms modulation of their mechanosensitivity.

2.4 Levels of melatonin in the serum and other biological fluids and organs

The pineal hormone melatonin is well-known synchroniser of the peripheral clocks by the central clock. However, melatonin is likely produced in mitochondria in neurons and other cells of the body, participating in the maintenance of cellular oxidant-antioxidant homeostasis (Maldonado et al., 2016; Reiter et al., 2017). Whilst the maximum concentration of melatonin at

night in blood serum is around 1nM in humans (Zdunska et al., 2021), many researchers consider concentrations of up to 1μM as still physiological (Acuna-Castroviejo et al., 2014; Maldonado et al., 2016). The reason for that is that the concentration of melatonin found in many biological fluids is significantly higher than that in the serum. For example, in cerebrospinal fluid, the concentration of melatonin is 4 times higher than in the plasma (Reiter et al., 2014), while the concentration of melatonin in the bile could be 1000 times more than that in the day-time serum (Tan et al., 1999). This is because many cells in the body have both enzymes (arylalkylamine-N-acetyltransferase and hydroxyindole-O-methyltransferase) that are required for melatonin synthesis from tryptophan, and thus can locally produce melatonin, which then can act as a paracrine biologically active substance (Carrillo-Vico et al., 2004; Pontes et al. 2006; Markus et al., 2013; Reiter et al., 2017). These include enterochromaffin cells in the gut mucosa, hepatocytes, retinal photoreceptors, immune cells (such as T-cells, macrophages, mast cells), spermatocytes, and cells in the skin (Carrillo-Vico et al., 2004; Pontes et al. 2006; Acuna-Castroviejo et al., 2014; Labrecque and Cermakian, 2015; Blasiak et al., 2016; Gonzalez-Arto et al., 2016; Maldonado et al., 2016; Reiter et al., 2017; Slominski et al. 2018). For example, in the gut, levels of melatonin are independent of pineal levels (Bubenik and Brown, 1997) and its concentration could be up to 400 times higher than that in the pineal gland (Konturek et al., 2007). Interestingly, the extrapineal levels of melatonin found in different peripheral organs and tissues do not demonstrate circadian variations (Bubenik, 2002; Konturek et al., 2007; Acuna-Castroviejo et al., 2014). Locally produced melatonin is likely play important role in physiological regulation of cell homeostasis due to its profound general antioxidative actions but also as tissue specific local paracrine factor (Dubocovich and Markowska, 2005; Galano et al., 2011; Acuna-Castroviejo et al., 2014; Zhang and Zhang, 2014). So far, there is no data available whether melatonin can be locally produced within the bladder wall. One of the potential sources of locally produced melatonin in the bladder are mast cells. There is dense network of resident mast cells in the lamina propria and detrusor muscle (Kim, 2016), which express MT1 and MT2 receptors and are capable of synthesising melatonin (Maldonado et al., 2010; Maldonado et al., 2016).

2.5 Effect of melatonin on the bladder function

MT1 and MT2 receptors are expressed on plasma membranes of neurons in the peripheral nervous system and CNS, and cells in peripheral organs and tissues such as the heart, lung, gut, kidneys, bladder, and immune cells. Some of the action of melatonin is due to its effects on nuclear receptors of the ROR family or directly on intracellular proteins including quinone reductase 2, and Ca^{2+} binding proteins since melatonin is membrane permeable (Dubocovich and Markowska, 2005; Pandi-Perumal et al., 2008; Hardeland et al., 2011; Emet et al., 2016). The effects of melatonin on the bladder function may involve a variety of different mechanisms including its central CNS and peripheral effects via plasma membrane MT receptors and/or intracellular effects (Semercioz et al., 2004; Matsuta et al., 2010; Han et al., 2012; Ramsay and Zagorodnyuk, 2022). The half-life of melatonin after intravenous infusion is around 20-30 min (Mallo et al., 1990; Claustrat et al., 2005). Melatonin has a high safety profile in humans (Galley et al., 2014; Andersen et al., 2016) and does not show any significant side effects even in high doses, except from some mild soporific, hypothermic, and hypotensive effects (Macchi and Bruce, 2004).

Early studies reported the presence of melatonin in the urine which peak during inactive phases in humans and rats (Lynch et al. 1975a, 1975b; Ozaki et al., 1976). It was also reported that melatonin was still present in the urine of rodents following a pinealectomy, suggesting a potential peripheral, local production (Lynch et al., 1975a; Ozaki and Lynch, 1976). However, it has been reported that rodents have a second pineal lobe which likely still releases melatonin after ablation of the main pineal lobe (Moller and Baeres, 2002). It has been demonstrated that rhythms of urine melatonin levels exhibit sex differences with rhythms in males having a lower amplitude compared to females (Gunn et al., 2016).

Central, intracerebral administration of melatonin in low doses (0.4-40 pmols) increases bladder capacity in rats. This was mediated via GABA-A receptors since bicuculline inhibited it (Matsuta et al., 2010). Activation of GABA-A receptors inhibits micturition accompanied by increased bladder capacity (Igawa et al., 1993; Kanie et al., 2000). This data suggests that melatonin's central inhibition of the micturition reflex is due to reinforcement of the brain inhibitory GABAergic neuronal activity. It is still unknown whether MT1/MT2 receptors are involved in this effect. This action is likely of physiological significance since doses of centrally administered melatonin that affect bladder capacity are within the rage of melatonin fluctuation in the plasma (Matsuta et al., 2010; Zdunska et al., 2021).

There is little information regarding the direct effects of melatonin on the bladder itself. It has been demonstrated that melatonin pre-treatment (2.5 mg/kg/day for 28 days orally) has no effect on isolated contractions of detrusor muscle strips *ex vivo* in adult female guinea pigs (Gomez-Pinilla et al., 2008). In isolated detrusor muscle strips from rats, melatonin in a concentration-dependent manner (0.01-1 μM) inhibited contractions of isolated rat detrusor muscle strips induced by electrical field stimulation, high K^+, and the L-type Ca^{2+} channel opener, Bay K 8644 (Han et al., 2012). Interestingly, this effect was not affected by the non-selective MT1/MT2 melatonin receptor antagonist, luzindazole, suggesting possible intracellular mechanism of melatonin's action. Previously, it was shown that melatonin can bind to Ca^{2+}-activated calmodulin with high affinity and may prevent it from activating myosin light-chain kinase, leading to decreased contractility of smooth muscle in the rat myometrium (Ouyang and Vogel, 1998; Ayar et al., 2001). It is likely that direct inhibitory effect of melatonin in the rat detrusor strips is via inhibition of the voltage-gated Ca^{2+} channels and through inhibition of the calmodulin/CaMKII system (Han et al., 2012). In the guinea pig bladder, melatonin also inhibits high K^+ and acetylcholine-induced contractions of isolated detrusor strips, however with IC_{50}=93μM (Semercioz et al., 2004), indicating pharmacological rather than physiological effects. Overall, these variable effects of melatonin on the bladder contractility are likely due to the different mechanism of action *in vivo* versus *ex vivo*, different route of administration, dose, age, sex, and species differences.

2.6 Effect of melatonin on bladder afferents

It has been recently revealed that melatonin concentration-dependently (10-100μM) inhibited the mechanosensitivity of stretch-sensitive low threshold muscular-mucosal afferents but not mucosal stretch-insensitive afferents in the guinea pig bladder (Ramsay and Zagorodnyuk, 2022). This inhibitory effect was due to activation of MT2, but not MT1, receptors on bladder afferents since MT2 antagonists, 4-P-PDOT and K-185, but not MT1 antagonist S26131 (Boutin et al., 2020), were able to abolish it. The data agrees with recent findings on the mouse DRG, demonstrating that MT2, but not MT1 receptor, were expressed on DRG neurons while MT1 receptors were present on glial cells (Lin et al., 2017). At high doses (30-100 μM) melatonin had an inhibitory action on detrusor muscle seen as an increase in bladder compliance evoked by

stretch. Afferent firing rate, induced by stroking of receptive field with von Frey hairs, was reduced by 10μM of melatonin. This indicates that melatonin has a direct effect on the mechanosensitivity of this class of afferents, thus inhibiting sensory signaling from the bladder, independently from its effect on detrusor muscle (Ramsay and Zagorodnyuk, 2022). Numerous studies demonstrated involvement of the cAMP second messenger system in the action of melatonin since activation of both MT1 and MT2 receptors inhibited forskolin-stimulated cAMP production in many tissues and cells (Reppert et al. 1995; Ekmekcioglu, 2006; Pandi-Perumal et al., 2008). It is likely that the inhibitory action of melatonin on bladder afferents via MT2 receptors involves a decrease in cAMP levels in sensory nerve fibres since melatonin prevented forskolin-induced increase in spontaneous activity and mechanosensitivity of low threshold muscular-mucosal bladder afferents (Ramsay and Zagorodnyuk, 2022). Like the effect on detrusor smooth muscle, the inhibitory effect of melatonin on stretch-sensitive bladder afferents is an example of melatonin acting as potent pharmacological agent. These inhibitory peripheral effects of melatonin on detrusor contractility and bladder afferents mechanosensitivity could be important as potential novel treatments of common bladder disorders.

2.7 Disruptions of bladder circadian rhythms and nocturia

The synchronisation of the circadian system with the external environment is vital for the health and survival of an organism. Therefore, it is not surprising that circadian rhythms play a pivotal role in regulating of the function of many visceral organs within the body. Furthermore, disruption of circadian rhythms may lead to various disorders or significantly exacerbate them. It has been suggested that the circadian rhythms disturbances, including impaired peripheral circadian rhythms in the bladder, melatonin production and sleep disturbance, could be one of the major causes of the nocturia (Drake et al., 2004; Sugaya et al., 2007; Noh et al., 2011; Negoro et al., 2012; Negoro et al., 2013; Noh et al., 2014; Obayashi et al., 2014; Ihara et al., 2017; Ihara et al., 2021).

Nocturia, or frequent night-time urination, is defined as waking up at night one or more times to void (Abrams et al., 2003). However, based on degree of bother, clinically significant nocturia is classified as two or more voiding episodes per night (Fiske et al., 2004; Brunner and Riss, 2011; Weiss et al., 2013). Nocturia is multifactorial condition that associated with variety of

chronic medical conditions such as cardiovascular disease, diabetes, and anxiety. Its major underlying pathophysiological changes include diurnal polyuria, nocturnal polyuria, and bladder storage problems (Brunner and Riss, 2011; Weiss et al., 2011; Weiss, 2012).

Nocturia affects 60-90% of the elderly population (Yoshimura, 2012; Bosch and Weiss, 2013). In the elderly, nocturia is associated with an increased risk of hospitalisation or death resulting from falls and fractures (Burgio et al., 2010), with more than 80% of falls and fractures in the elderly occurring due to night-time movement (Latimer Hill et al., 2007).

Nocturia is becoming increasingly prevalent in younger individuals; up to 11-44% of both women and men aged 20 to 40 years report 1 or more voids per night (Bosch and Weiss, 2013; Weiss et al., 2013, Zumrutbas et al., 2016). It has been also shown that nocturia is associated with increased symptoms of bother and an increased prevalence of depression, especially in younger men and women (Kupelian et al., 2012). It is likely that the increase in nocturia prevalence in the younger population is due to the increasing practice of shift work; nearly 30% of the working population is employed on a shift work basis (Kim et al., 2014). The exact mechanisms on how this contributes to the increasing prevalence of nocturia are still not clear. For example, in a pilot study no changes in functional bladder capacity were observed during the night in rotational shifts nurses (Kim et al., 2014). However, in large-scale studies, it has been demonstrated that at night bladder capacity was decreased in shift workers, without urine production being affected (Kim, 2016b). In lieu of shift work, there are other numerous factors that can lead to the development of nocturia including psychosocial variables, sleep disturbances, presence of overactive bladder, and benign prostatic hyperplasia.

Nocturia is a frequent urinary symptom of overactive bladder syndrome and bladder outlet obstruction due to benign prostatic hyperplasia (Drake, Mills et al., 2004; Espuna-Pons et al., 2010; Weiss et al., 2011). However, treatment of these conditions with antimuscarinics, alpha blockers, and 5-alpha reductase inhibitors, did not have clinically significant effects on nocturia symptoms (Smith and Wein, 2011).

2.8 Melatonin in the treatment of LUT symptoms and bladder disorders

Changes in endogenous melatonin production as well as alterations in MT1 and/or MT2 receptor expression have been identified in circadian rhythm sleep disorders and many other diseases such as Alzheimer's and Parkinson's diseases, glaucoma, depression, and different types of cancer (Pandi-Perumal et al., 2008; Hardeland et al., 2011; Li et al., 2017; Talib et al., 2021). Melatonin has been suggested as potential treatment of LUT symptoms developed in many common bladder disorders and in the elderly.

2.8.1 Melatonin and LUT symptoms of the aged bladder

LUT dysfunction is a major cause of morbidity and decreased quality of life in the elderly. Storage and voiding abnormalities in the elderly may include bladder outlet obstruction, detrusor overactivity, and impaired detrusor contraction (Benson, 1990; Hald and Horn, 1998; Gomes et al., 2004; Poeggeler, 2005).

It is well established that oxidative stress, which is mainly due to accumulation of reactive oxidative species (ROS, O_2^-, OH^-, H_2O_2) and reactive nitrogen species (nitric oxide and peroxynitrite), is a key hallmark of ageing and the development of chronic diseases (de Almeida et al., 2022; Xu et al., 2022). Recent studies have been shown that exacerbated oxidative stress during aging may cause significant functional and structural changes in the bladder. It has been demonstrated that accumulation of ROS is significantly augmented in the aged bladder (Nocchi et al., 2014). It has been also shown that in aged mouse bladder, stretch-induced firing of low threshold bladder afferents is enhanced compared to adult animals (Daly et al., 2014). One the major targets of free radicals in the bladder are sensory nerves. ROS (in particularly H_2O_2) significantly increase excitability of bladder afferents acting predominantly via TRPA1 channels (Nicholas et al., 2017). All this may lead to the development of LUT symptoms such as excessive urgency, frequency and nocturia in the elderly.

Melatonin is a well-known free radical scavenger and anti-inflammatory agent that acts to stabilise cell membranes, making them less susceptible to oxidative insult and ultimately suppressing inflammatory reaction (Galano et al. 2011; Mauriz et al., 2013). Ameliorating neuroinflammation and neurodegeneration via decreasing ROS levels and downregulation of pro-inflammatory mediators, enzymes and cytokines are well established effects of melatonin in aging mouse models (Ali et al., 2015). Since melatonin is a potent free radical scavenger and possesses antioxidant, anti-inflammatory and anti-apoptotic properties (Hardeland et al., 2011; Mauriz et al.,

2013; Zhang and Zhang, 2014; Favero et al., 2017), it has the potential to be a safe and effective treatment for age-related changes in detrusor contractility and bladder afferent mechanosensitivity. It has been documented that melatonin pre-treatment (2.5 mg/kg/day for 28 days orally) restored neuromuscular function and impaired bladder contractility of detrusor muscle *ex vivo* in aged animals by normalizing Ca^{2+} signalling and increasing Ca^{2+} sensitisation most likely via its effect on cytosolic and mitochondrial oxidative stress (Gomez-Pinilla et al., 2007; Gomez-Pinilla et al., 2008). This treatment also led to significant improvement of age-induced changes in bladder function *in vivo* by reversing the decreased residual volume and micturition pressure, and detrusor overactivity induced by aging (Gomez-Pinilla et al., 2007). The effect of melatonin in this case could be due to the recovery of circadian rhythms, general improvement of physiological functions, and/or direct local antioxidant effect of melatonin improving bladder contractility of aged animals (Gomez-Pinilla et al., 2008).

2.8.2 Melatonin and overactive bladder syndrome

Overactive bladder (OAB) syndrome is a debilitating condition which affects urine storage and is characterised by a mixture of LUT symptoms, including urgency, frequency, nocturia and, in many cases, urge incontinence, in the absence of any urinary tract infection (Haylen et al., 2010; Truzzi et al., 2016). Men and women are similarly affected by the OAB with the prevalence ranging between 7 to 9% and 16 to 26%, respectively (Tikkinen et al., 2007; Irwin et al., 2011; Truzzi et al., 2016). With an ageing population, OAB will inevitably increase in prevalence, representing a huge challenge for the health care system (Madersbacher et al. 2004; Irwin et al., 2011; Truzzi et al., 2016; Durden et al., 2018). Bladder overactivity is not life-threatening, however, the social isolation caused by incontinence, fear of incontinence, urgency and frequency have debilitating impact on quality of life (Stewart et al., 2003; Truzzi et al., 2016). Many hypotheses were put forward explaining the mechanisms of bladder overactivity including myogenic, neurogenic, autonomous, and urothelial, all of which directly or indirectly implicate overactivation of stretch-sensitive bladder afferents (Drake et al., 2001; Brading et al., 2004; de Groat and Yoshimura, 2009; Birder and Andersson, 2013; Fry and Vahabi, 2016; Grundy et al., 2018; Peyronnet et al., 2019; Zagorodnyuk et al., 2019). In rats, melatonin treatment suppressed hyperosmolar-induced bladder overactivity; inter-contraction interval and bladder capacity were

significantly increased while detrusor overactivity index and basal bladder pressure were decreased (Juszczak et al., 2011).

Symptoms of OAB in the elderly are associated with bladder ischemia due to age-related changes in the pelvic vasculature supplying the bladder and bladder outlet obstruction (Andersson et al., 2017). In aging men, symptoms of OAB are often due to the bladder outlet obstruction that can affect up to 22% of the worldwide population (Irwin et al., 2011). In the USA, it is estimated that approximately 50% of men at the age of 60 have histological benign prostatic hyperplasia and almost 75% men in their 70s develop benign prostatic hyperplasia, associated with progressive LUT symptoms (Wei et al. 2005; Xu et al., 2022). It has been proposed that bladder wall ischemia is a likely predisposing factor for bladder overactivity (Brading et al., 2004). Numerous preclinical studies on laboratory animals showed that pelvic arterial insufficiency and bladder outlet obstruction results in bladder ischemia leading to oxidative stress. An overproduction of ROS and reactive nitrogen species released by leukocytes, endothelial cells, and smooth muscle cells induces morphological damage and neurodegeneration within the bladder wall (Lemack et al., 2000; Azadzoi et al., 2010; Turer and Hill, 2010; Nomiya et al., 2012; Xu et al., 2022). Focal regions of hypoxia with normal or increased blood flow in compensated bladder obstruction (or decreased blood flow in decompensated stage), are well documented in animal models of bladder outlet obstruction (Schroder et al., 2001; Ghafar et al., 2002; Scheepe et al., 2011). This likely results in patchy nerve degeneration seen in obstructed bladder in both animals and humans (Levin et al., 2000; Brading et al., 2004). In the guinea pig obstructed overactive bladder, enhanced sensory signalling from the bladder is due to increased firing of low threshold stretch-sensitive afferents induced by increased local non-voiding contractions, and by sensitised high threshold afferents (Zagorodnyuk et al., 2019).

Preclinical *in vivo* rat studies demonstrated that pre-treatment with melatonin protects the bladder against sepsis- and ischemia-induced oxidative damage (Paskaloglu et al. 2004; Nomiya et al., 2013). Thus, melatonin could be beneficial for the treatment of symptoms of OAB due to (i) its central effect of increasing bladder capacity (Matsuta et al., 2010), (ii) inhibitory effects on detrusor contractility (Semercioz et al., 2004; Han et al., 2012; Ramsay and Zagorodnyuk, 2022) and stretch-sensitive bladder afferents (Ramsay and Zagorodnyuk, 2022), and (iii) potent

beneficial effects against bladder ischemia since melatonin is a free radical scavenger and has powerful antioxidative properties.

2.8.3 Melatonin and nocturia

Nocturia, with 2 or more voids/night, affects approximately one third of patients with OAB for both sexes (Irwin et al., 2006). Melatonin has demonstrated benefits in ameliorating the symptoms of nocturia. Endogenous melatonin levels decrease as we age (Obayashi et al., 2014), and night serum melatonin levels in elderly persons with nocturia are lower than those without (Sugaya et al., 2008), making it a popular treatment for nocturia. Melatonin treatment (2mg daily) significantly decreased nocturnal urination frequency and improved quality of life (Sugaya et al., 2007; Leerasiri et al., 2022). This reduction in nocturia symptoms is also seen in patients with nocturia caused by bladder obstruction due to benign prostatic hyperplasia (Drake et al., 2004) and Parkinson's disease (Batla et al., 2021). The function of melatonin as a circadian rhythm synchroniser in many organs and tissues is well established (Pandi-Perumal et al., 2008; Hardeland et al., 2011). One may speculate that the ameliorating effect of melatonin on nocturia may involve its direct effect on peripheral clock genes in the bladder, as this was suggested in other tissues (Hardeland et al., 2011; Brzezinski et al., 2021). Although, no data is yet available on the potential direct effect of melatonin on the peripheral circadian system in the bladder.

2.8.4 Melatonin and interstitial cystitis/ bladder pain syndrome

Interstitial cystitis (commonly referred to as bladder pain syndrome) is a chronic bladder syndrome characterised by pelvic and bladder pain, urinary frequency and urgency, and nocturia (Jones and Nyberg, 1997; Bogart et al., 2007; Parsons, 2007, McLennan, 2014; Grundy et al., 2018; Birder, 2019). Early symptoms of interstitial cystitis are present in up to 13% of the population with significantly higher prevalence seen in women (Rosenberg et al., 2007). Painful bladder syndrome has a significant impact on quality of life. It causes painful sensations similar to urinary tract infection, but cultures detect no infectious agents (Parsons, 2007; Yoshimura et al., 2014). The aetiology of bladder pain syndrome is still unknown but epithelial dysfunction, inflammatory or bacterial products, autoimmune factors, and sensory and/or central abnormalities may be involved (Denson et al., 2000; Ness et al., 2005; McLennan, 2014; Yoshimura et al., 2014). Current therapies such as intravesical instillation of DMSO, heparin or pentosan polysulfate, and botulinum toxin A, low dose antidepressants and antihistamines are far from satisfactory due to

limited efficacy and significant side effects. This is unsurprising as these treatments do not target the underlying cause of the disease, which is poorly understood (Dawson and Jamison, 2007). Together OAB and bladder pain syndromes affect approximately 16% of western population and have a significant economic impact of more than $70 billion annually in the USA alone (McLennan, 2014, Pierce and Christianson, 2015, Truzzi et al., 2016; Durden et al., 2018).

Studies in animal models suggest the potential for melatonin to treat symptoms of interstitial cystitis (Zhang et al., 2013). In animal models of bladder pain syndrome such as experimental cystitis induced by protamine sulfate or cyclophosphamide, melatonin treatment reduced the abnormal bladder morphological changes in the bladder mucosa, oxidative stress, inflammatory cytokines, expression of substance P, and improved LUT symptoms and signs by reducing the frequency of voiding (Cetinel et al., 2003; Topal et al., 2005; Dobrek and Thor, 2011; Zhang et al., 2013; Chen et al. 2014). In addition to melatonin's free radical scavenger and antioxidative properties, the anti-inflammatory mechanisms of melatonin to ameliorate symptoms of interstitial cystitis could involve its ability to downregulate mast cell activation. Melatonin in physiological doses has significant direct inhibitory effects on the activation and proliferation of mast cells via MT1 and MT2 receptors (Izzo et al., 2004; Maldonado et al., 2010; Zhang et al. 2013; Maldonado et al. 2016). It is worth mentioning that mast cell infiltration in the lamina propria is one of the important pathological biopsy features used for diagnostic criteria of interstitial cystitis/ bladder pain syndrome (Tomaszewski et al., 2001; Leiby et al., 2007; Kim 2016a).

The summary of mechanisms of action of melatonin on the bladder function in health and diseases is illustrated in Fig. 2.

3. Conclusions

The central and peripheral circadian systems regulate a wide array of functions of many visceral organs including urinary bladder. Disruptions of these rhythms can cause organ disorders or exacerbate pre-existing ones. Due to this, some diseases should be considered, and treated as, disorders of circadian rhythms. It has been suggested that nocturia, developed mainly in the elderly, could be one of these circadian rhythm related disorders. Many types of gap junctions and ion channels in the detrusor, urothelium, and sensory nerves innervating the bladder are likely under strict local peripheral circadian system control. Melatonin is proving to be beneficial in the treatment of many circadian related disorders including nocturia. The ameliorating effect of

melatonin on bladder function is due to multiple mechanisms. This includes its central effects on voiding, peripheral inhibitory effects on detrusor contractility and bladder afferents, and its strong antioxidative effects. More preclinical studies are warranted to determine the mechanisms of circadian rhythms of voiding and the role of melatonin as physiological regulator of bladder function and its usefulness as potential pharmaceutical agent for the treatment of the LUT symptoms of aged bladder. This may also open a novel avenue for treatment of common bladder disorders such as overactive bladder and bladder pain syndromes.

Data availability

No data was used for the research described in the article

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Figures

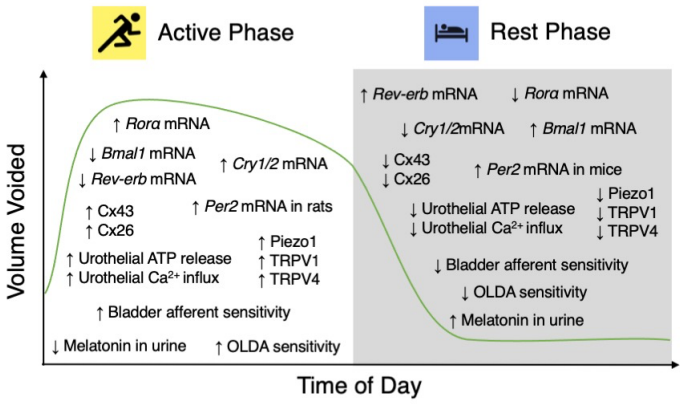

Fig. 1. Summary of the major mechanisms of circadian rhythms regulation of the bladder function. Circadian system with master clock located in the suprachiasmatic nucleus of the hypothalamus and peripheral clock within the bladder wall and dorsal root ganglion neurons, powerfully modulates 24hr rhythms of the bladder urine storage and voiding in mammals by increasing voiding volume during their active phases and decreasing it during inactive phases. The major underlying mechanisms include time of a day dependent melatonin secretion by pineal gland and its effect on the bladder capacity, and circadian dependent oscillation in the activity of peripheral clock genes within the bladder wall and dorsal root ganglia resulting in up- or downregulation of variety of ion channels and changes in communication between cells in the bladder via gap junctions.

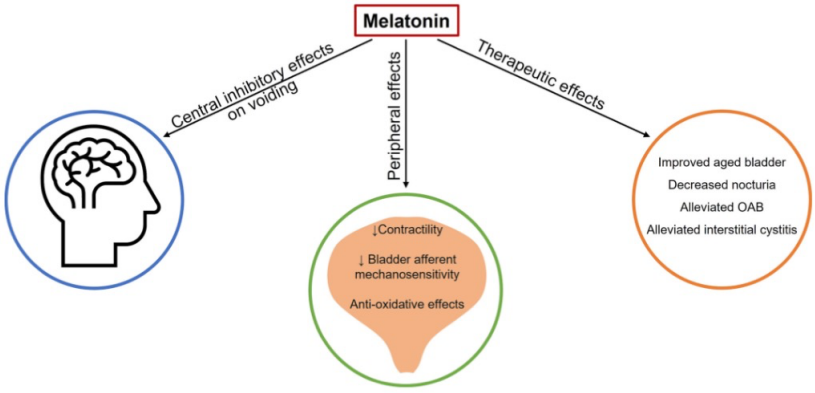

Fig. 2. Mechanism of action of melatonin on the bladder function. Melatonin produced by the pineal gland or taken as supplements has central and peripheral effects on the bladder. It has central inhibitory effect on brain micturition pathways resulting in increased bladder capacity. Peripheral effect of melatonin includes inhibition of detrusor contractility and mechanosensitivity of the low threshold stretch-sensitive bladder afferents. It has also strong antioxidative effect on the bladder. Melatonin could be used as potential treatment of many bladder pathologies ameliorating LUT symptoms and contractility of aged bladder, decreasing nocturia and alleviating symptoms of OAB and interstitial cystitis.