Therapeutic insights and molecular mechanism linking melatonin signaling and membranous nephropathy (Review)

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Abstract. Endogenous melatonin is synthesized at night by specific enzymes and exerts various physiological effects through both melatonin receptor-dependent and -independent pathways. Moreover, exogenous melatonin has been demonstrated to have pleiotropic therapeutic effects on a range of pathological conditions, including renal diseases. The melatonin signaling pathway involves specific enzymes responsible for melatonin synthesis and cellular responses mediated by melatonin, which are evolutionarily conserved in both brain and peripheral tissues. Although the physiological functions of the melatonin-mediated signaling pathway are well-documented across multiple organ systems, its effects on the kidney are less recognized. The present review summarizes the expression levels of melatonin biosynthesis enzymes and melatonin receptors, as well as their roles in renal tissue under pathological conditions such as membranous nephropathy (MN). The present review explores the molecular mechanisms regulating the expression of aryl-alkyl-amine N-acetyl-transferase, nuclear enriched abundant transcript 1 and melatonin receptor 1A (MTNR1A) in renal tubular epithelial cells. Overall, the present review provides new insights into the role of MTNR1A in the pathology, treatment and prevention of MN.

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Abbreviations: MN, membranous nephropathy; CKD, chronic kidney disease; DN, diabetic nephropathy; ESRD, end-stage renal disease; TPH, tryptophan hydroxylase; DDC, aromatic amino acid decarboxylase; AANAT, aryl-alkyl-amine N-acetyltransferase; HIOMT, hydroxy-indole-O-methyltransferase; SCN, suprachiasmatic nucleus; TECs, tubular epithelial cells; CREB, cAMP responsive element binding protein; MTNR1A, melatonin receptor 1A; MTNR1B, melatonin receptor 1B; RORα, retinoic acid receptor-related orphan receptor alpha; VDR, vitamin D receptor; QR2, quinone reductase 2; cAMP, cyclic adenosine monophosphate; PKC, protein kinase C; IP3, inositol 1,4,5-triphosphate; PKG, protein kinase G; PLCb, phospholipase C beta; PITX1, pituitary homeobox-1; PER2, period 2; pCREB, phosphorylated-CREB; hnRNPL, heterogeneous nuclear ribonucleoprotein L; SNPs, single nucleotide polymorphisms; Xist, X inactive specific transcript; MN-melatonin, MN mice treated with exogenous melatonin; LPS, lipopolysaccharide; 6-SMT, 6-sulphatoxymelatonin; lncRNAs, long non-coding RNAs; NEAT1, nuclear enriched abundant transcript 1

Key words: melatonin, AANAT, NEAT1, MTNR1A, renal TECs, MN

Contents

1. Introduction

Melatonin (N-acetyl-5-methoxy-tryptamine) is an amphiphilic tryptophan-derived indoleamine highly conserved among vertebrates (1). Although melatonin is primarily synthesized in the pineal gland, smaller amounts are detected in peripheral tissues, including the gastrointestinal tract, skin, retina and bone marrow (2,3). The release of melatonin from the pineal

gland is rhythmically regulated by retinal photoreceptors, with low levels during the day and high levels at night (4). Melatonin cannot be stored in tissues and is immediately released into the blood to modulate physiological conditions in peripheral tissues (5). Therefore, melatonin has a short half-life of 30-60 min in the body (6). Melatonin regulates several physiological functions, including circadian rhythm regulation, acting as an antioxidant and free radical scavenger, possessing anti-inflammatory properties, modulating mitochondrial homeostasis, and enhancing nitric oxide bioavailability (7).

A total of four enzymes involved in the melatonin synthesis pathway, tryptophan hydroxylase (TPH), aromatic amino acid decarboxylase (DDC), aryl-alkyl-amine N-acetyl-transferase (AANAT) and hydroxy-indole-O-methyl-transferase (HIOMT), are primarily expressed with a circadian rhythm in the suprachiasmatic nucleus (SCN), pineal gland and retina (Fig. 1) (8). TPH and DDC sequentially catalyze the conversion of tryptophan to serotonin, which is a precursor to melatonin (9). AANAT converts serotonin to N-acetyl-serotonin, which is then converted to melatonin by HIOMT (10). Melatonin modulates diverse physiological conditions via a combination of both melatonin receptor-mediated and receptor-independent mechanisms (11). Specifically, melatonin receptor activation plays a pivotal role in regulating circadian gene expression, thereby influencing the sleep-wake cycle, body temperature, blood pressure, metabolism, urine production and hormone secretion (12). Conversely, the receptor-independent actions of melatonin are largely attributed to its potent free-radical-scavenging and antioxidant properties. The electron-rich aromatic indole ring in melatonin makes it a potent electron donor, significantly reducing oxidative stress (13). This direct interaction with reactive oxygen species allows melatonin to protect cellular components from oxidative damage, contributing to its broad protective effects (14). In general, melatonin binds with high affinity and specificity to membrane receptors in the brain and periphery to trigger physiological responses by altering cell signaling pathways (15).

The melatonin signaling pathway consists of melatonin synthesis enzymes and melatonin-mediated cellular responses, which are evolutionarily conserved in both brain and peripheral tissues. However, most studies focus on the role of the melatonin signaling pathway in brain tissue. In the present review, the expression of melatonin signaling components and their mediated roles in renal tissue under various biological conditions are discussed, and evidence regarding the benefits of targeting membranous nephropathy (MN) with this approach is presented. The present review offers new insights into the melatonin signaling pathway in the pathology, treatment, and prevention of nephropathy.

2. Melatonin synthesis enzyme in kidney

Melatonin, a small amphipathic indolamine, is ubiquitous across nearly all organisms, from bacteria to humans, and plays a crucial role in regulating circadian rhythms and sleep-wake cycles (16). The circadian production of melatonin is regulated by endogenous oscillators within the body and synchronized by daily and seasonal variations in the environmental light-dark cycle (17). The pineal gland and SCN are the major sources of melatonin in vertebrates, and they appear to regulate target cells via an exocrine mechanism (18). Most of the research on the gene expression of melatonin-synthesizing enzymes focuses on retinal cells and pinealocytes, with limited research specifically focused on the kidney (19). In the present review, focus was addressed on the expression levels of the four enzymes of the melatoninergic pathway (TPH, DDC, AANAT and HIOMT) in central and peripheral locations of human tissue using data from The Human Protein Atlas (20,21). Although TPH and DDC contribute to melatonin synthesis, they also play roles in other physiological processes independent of melatonin production. The results indicated that the top three tissues with the highest expression of TPH are the rectum, stomach and small intestine; the highest expression of DDC is found in the kidney, retina and small intestine; the highest expression of AANAT is found in the retina, choroid plexus and testis; and the highest expression of HIOMT is found in the choroid plexus, epididymis and pituitary gland (Fig. 2). Consistent with previous findings, melatonin biosynthesis enzymes are identified in the retina, pituitary gland, and gastrointestinal tract (22,23). Notably, the kidney exhibited low expression levels of TPH, AANAT, and HIOMT, and the highest levels of DDC (Fig. 2). These results suggest that melatonin-synthesizing enzymes are expressed in renal tissue. However, there are a few concerns regarding these results from The Human Protein Atlas (20,21). First, the kidney consists of different cell types organized into sub-anatomical tissue structures. These melatonin synthesis genes could be expressed in immune cells or other cell types within renal tissue. Moreover, RNA expression does not necessarily represent protein production in the kidney. Although the highest levels of DDC have been noticed in the kidney, it is important to note that DDC is not solely responsible for melatonin production. DDC protein also catalyzes the decarboxylation of L-3,4-dihydroxyphenylalanine to dopamine, L-5-hydroxytryptophan to serotonin, and L-tryptophan to tryptamine (24). Collectively, whether these melatonin synthesis enzymes produce melatonin in the kidney needs to be further validated.

Previous studies showed that AANAT transcripts and melatonin can be detected in renal tubular epithelial cells (TECs) in both human cells and mouse kidneys (25,26). The molecular mechanism indicated that cAMP responsive element binding protein (CREB) increases AANAT transcriptional activity in TECs, while it is decreased by c-Fos. The c-Fos family forms the activator protein-1, functioning as transcriptional activators or repressors depending on the diverse collection of interacting proteins (27). Functional results revealed that AANAT expression is decreased by c-Fos, leading to enhanced cell damage in an albumin-injury cell model. Notably, melatonin levels increased from 10 to 100 pg/ml following c-Fos knockdown in the TEC cell line HK-2 (25). Although these results suggest that TECs produce melatonin *in vitro*, the precise niche within renal tissue still needs to be confirmed. Melatonin metabolism is mostly metabolized in the liver and kidneys by several enzymes of the cytochrome P450 system (28,29). Although only a small percentage (<5%) of blood melatonin is unmetabolized and excreted into the urine (30), these unmetabolized melatonin could be identify in renal tissue. Therefore, the specific knock-out of AANAT or HIOMT in glomerular or

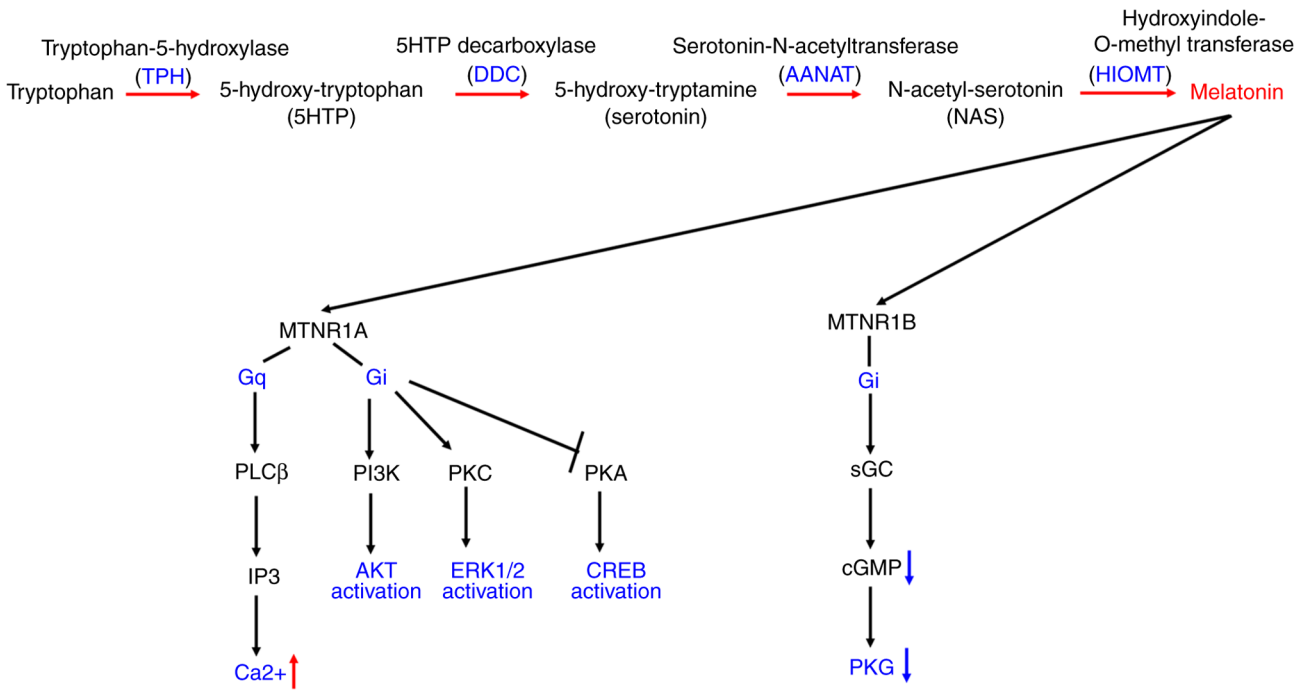

Figure 1. Diagrammatic representation of the melatonin synthesis pathway and melatonin receptor-mediated cell signaling. The metabolic pathway converting tryptophan to melatonin involves the enzymes TPH, DDC, AANAT and HIOMT (also known as ASMT). Melatonin activation of MTNR1A receptors triggers Gq activation, leading to increased levels of calcium and IP3. Additionally, it induces Gi-dependent activation of the PI3K/AKT and PKC/ERK pathways, while causing Gi-dependent inactivation of the PKA/CREB axis. MTNR1B coupling to Gi results in PKG inactivation and a decrease in intracellular cGMP levels. TPH, tryptophan hydroxylase; DDC, aromatic amino acid decarboxylase; AANAT, aryl-alkyl-amine N-acetyltransferase; HIOMT, hydroxy-indole-O-methyl-transferase; MTNR1A, melatonin receptor 1A; MTNR1B, melatonin receptor 1B; PKC, protein kinase C; cGMP, 3'-5'-cyclic guanosine monophosphate; PKG, protein kinase G; IP3, inositol 1,4,5-triphosphate; PLCb, phospholipase C beta.

TEC mice should be used to determine endogenous melatonin production.

3. Melatonin receptor and its mediated signaling

In higher vertebrates, the melatonin receptor family consists of two members, melatonin receptor 1A (MTNR1A) and melatonin receptor 1B (MTNR1B), both exhibiting high affinity for the natural ligand melatonin (Fig. 1) (31). The amino acid homology between human MTNR1A and MTNR1B is ~60% overall, with a higher similarity of ~73% within the transmembrane domains (31). Interestingly, the human MTNR1A receptor exhibits greater resemblance to the rodent MTNR1A than to the MTNR1B receptors found in bovine, ovine and porcine species (32). Other nuclear receptors with melatonin at low affinity include the retinoic acid receptor-related orphan receptor alpha (RORα) and the vitamin D receptor (VDR) (33,34). However, these results need replication to confirm the interaction between melatonin and RORAα and VDR in future studies. Moreover, the quinone reductase 2 (QR2) enzyme likely corresponds to the melatonin receptor binding site, binding melatonin in the μM range (35). Further studies are needed to identify the subcellular localization of QR2.

These high-affinity melatonin receptors are expressed in multiple tissues, including the heart and arteries, adrenal gland, kidney, lung, liver, gallbladder, small intestine, adipocytes, ovaries, uterus, breast, prostate, skin, lymphocytes and central nervous system (36). Melatonin receptors are derived from various tissues, with the highest density expressed in the SCN, retina and anterior pituitary (37). The coupling of high affinity melatonin receptors MTNR1A and MTNR1B varies in distribution throughout the body (38).

Both melatonin receptors couple to heterotrimeric G proteins of the Gi subfamily, resulting in decreased adenylyl cyclase activity and diminished cyclic adenosine monophosphate (cAMP) production (39). Therefore, melatonin signaling leads to the downregulation of genes controlled by the CREB protein (40). Melatonin receptors may also interact with other G proteins in a context-specific manner (41). Since the interaction between MTNR1A and Gi coupling exhibits higher affinity compared with MTNR1A-Gq coupling, MTNR1A activation primarily triggers the Gi/PKA/CREB, Gi/phosphatidylinositol 3'-kinase (PI3K)/AKT, Gi/protein kinase C (PKC)/ERK1/2, and Gq/phospholipase C beta (PLCβ)/inositol 1,4,5-triphosphate (IP3)/Ca^{2+} pathways (Fig. 1) (42). The binding of melatonin to MTNR1A stimulates PLC activity, leading to the conversion of phosphatidylinositol 4,5-biphosphate to diacylglycerol and IP3 (44). Elevated levels of these secondary messengers activate several kinases, including PKC, calmodulin kinases and mitogen-activated protein kinases (43). Activation of melatonin receptors leads to alterations in the ERK kinases' signaling pathway (44). However, MTNR1B activation decreases 3'-5'-cyclic guanosine monophosphate levels, leading to reduced protein kinase G activity (Fig. 1) (45). Moreover, the Gi subfamily exhibits slightly higher affinity in coupling to MTNR1A than to MTNR1B (46). In a physiological context, melatonin signaling

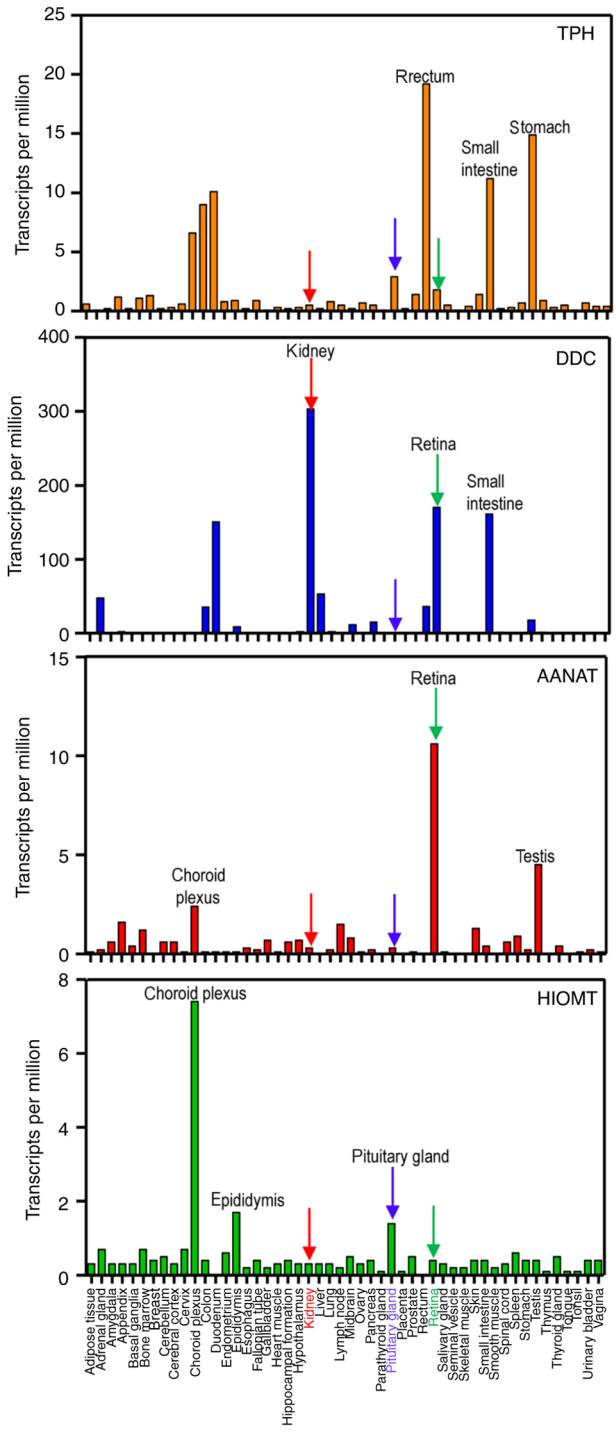

Figure 2. A comprehensive tissue-specific analysis of melatonin synthesis enzyme gene expression across 37 tissues. Transcripts per million on the y-axis represents the transcript quantification value, while the x-axis represents different tissues. This data is based on The Human Protein Atlas version 18.1 and Ensemble version 88.38 (21). TPH, tryptophan hydroxylase; DDC, aromatic amino acid decarboxylase; AANAT, aryl-alkyl-amine N-acetyltransferase; HIOMT, hydroxy-indole-O-methyl-transferase.

through MTNR1A and MTNR1B may differ. Notably, cells and tissues expressing receptors are not the only targets of melatonin's physiological actions, as melatonin also exerts non-receptor-dependent mechanisms of action, such as direct antioxidant effects through the chelation of oxygen radical species.

4. Melatonin receptor in kidney with MN

Both melatonin receptors are expressed in various types of organs and tissues (47). However, there is a different expression pattern in different cells within the same organ. For example, in adult human islet cells, MTNR1B receptor is expressed higher than MTNR1A in both α and β cells; the expression levels of MTNR1B is similar in α and β cells (48). The expression levels of melatonin receptors in the renal tissue were previously determined by the authors; the results revealed that MTNR1A is more highly and abundantly expressed in glomerular and TECs than MTNR1B (49). Notably, MTNR1A is expressed predominantly in TECs rather than in glomeruli at both the RNA and protein levels (49).

Membranous glomerulonephritis is an autoimmune-mediated glomerular nephritis characterized by subepithelial immune complex deposits. The majority of primary MN cases are caused by circulating antibodies that target the M-type phospholipase A2 receptor located on the podocyte membrane, triggering glomerular injury through a complement-dependent process (50). Since TEC injury occurs during the progression of MN, it often lacks a definitive cure and may progress to chronic kidney disease (CKD) and end-stage renal disease (ESRD), thereby posing a substantial public health threat (51). Collectively, averting the advancement of CDK or ESRD necessitates a more comprehensive mechanistic understanding of MN.

Few previous studies have documented that MTNR1A expression is decreased in various types of diseases, including the substantia nigra and amygdala in Parkinson's disease, as well as in human ductal breast cancer (52,53). Using both clinical and experimental MN kidneys, the expression of MTNR1A in TECs was validated. The downregulation of MTNR1A suggests a protective role against MN progression. To assess the role of reduced MTNR1A expression in MN progression, the biological effects of luzindole (a competitive antagonist of MTNR1A/MTNR1B) were evaluated in the MN mouse model. Consistent with previous findings, MN mice exhibited symptoms of proteinuria, hypercholesterolemia and hypoalbuminemia (54-59). Remarkably, the inhibition of the MTNR1A receptor using luzindole in MN mice exacerbated renal dysfunction, which was concomitant with the upregulation of the core clock gene period 2 (PER2) (49). The activating transcription factor 4 and CREB heterodimer is essential for the transactivation of the PER2 gene depending on cAMP stimulation (60), suggesting that luzindole blocks the MTNR1A-mediated cell signaling. However, luzindole may impact blood melatonin synthesis or other hormone production in different tissues, subsequently affecting cAMP production in the kidney. Therefore, the specific knockout of MTNR1A in mice TECs should be employed to elucidate the MTNR1A-mediated physiological condition and signaling pathway during the progression of MN.

5. Regulation of MTNR1A expression in renal TECs

Considering the documented downregulation of MTNR1A in MN, gaining a deeper understanding of its regulation will be crucial in delineating the pathogenesis of this condition and improving both diagnostic and therapeutic approaches.

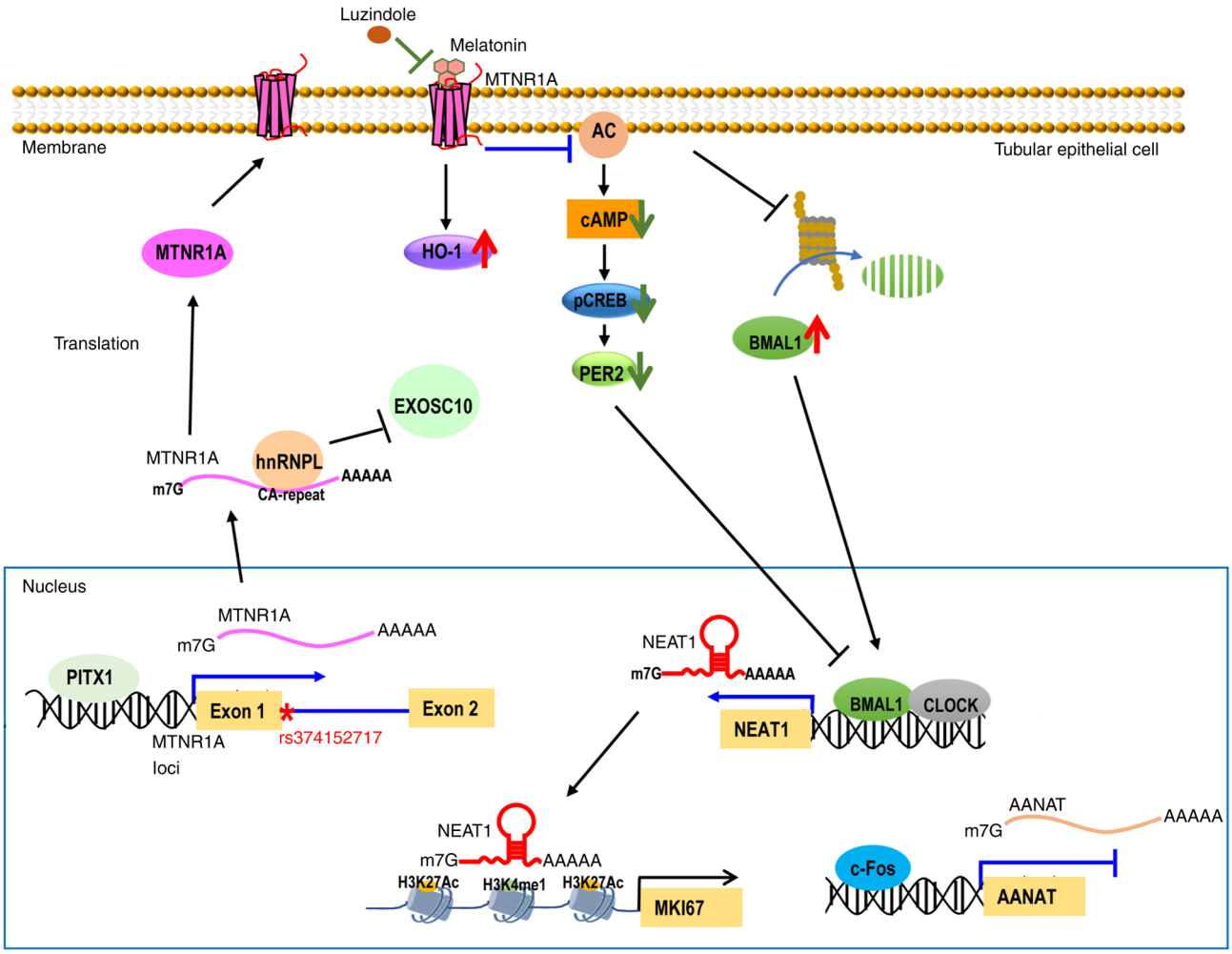

Figure 3. Schematic representation illustrates the molecular mechanism regulating MTNR1A, NEAT1 and AANAT gene expression in renal TECs. PITX1 transcriptionally upregulates MTNR1A expression, while c-Fos transcriptionally downregulates AANAT expression in the nucleus. AANAT is the rate-limiting factor for melatonin synthesis. Albumin treatment reduced the viability of TECs by decreasing PITX1 and increasing c-Fos. In the cytosol, hnRNPL binds to MTNR1A transcripts via CA-repeat elements, decreasing MTNR1A degradation by EXOSC10. Melatonin binding to MTNR1A triggers upregulation of HO-1 levels and downregulation of cAMP levels, phosphorylated CREB and PER2. Luzindole, an MTNR1A antagonist, decreased the MTNR1A-mediated signaling pathway. The long noncoding RNA *NEAT1* is increased by melatonin and exhibits circadian rhythm in TECs through whole gene identification. Melatonin enhances clock-controlled NEAT1 expression in TECs by stabilizing the BMAL1 protein. Elevated clock-controlled NEAT1 may regulate circadian genes, including MKI67, by influencing H3K27Ac and H3K4me1 occupancy at enhancer regions of target genes. Genomic location of MTNR1A single nucleotide polymorphism rs374152717 (*), a donor splice site variant in intron 1 near exon 1. MTNR1A, melatonin receptor 1A; NEAT1, nuclear enriched abundant transcript 1; AANAT, aryl-alkyl-amine N-acetyltransferase; TECs, tubular epithelial cells; PITX1, pituitary homeobox-1; hnRNPL, heterogeneous nuclear ribonucleoprotein L; HO-1, heme oxygenase-1; cAMP, cyclic adenosine monophosphate; CREB, cAMP responsive element binding protein; EXOSC10, exosome component 10.

Indeed, molecular mechanisms indicate that cytoplasmic heterogeneous nuclear ribonucleoprotein L (hnRNPL) exerts a stabilizing effect on the MTNR1A transcript through its interaction with MTNR1A RNA, serving to protect it from degradation by the exosome component 10 (EXOSC10) protein (Fig. 3) (26,61). EXOSC10 is an evolutionarily conserved nuclear protein that interacts with the RNA exosome complex and exhibits 3'-5'exoribonuclease activity (62). Furthermore, the activation of MTNR1A by pituitary homeobox-1 (PITX1) is upregulated at the transcriptional level (Fig. 3) (49,63,64). The predicted PITX1-binding region on the MTNR1A promoter, located between positions -545 and -426, has been examined. Chromatin immunoprecipitation-quantitative PCR results demonstrated significant PITX1 recruitment to this region (49). These findings indicate that PITX1 directly transactivates MTNR1A in renal TECs. TECs depleted of MTNR1A, PITX1 and CREB exhibit increased PER2 expression at both the RNA and protein levels compared with control cells, suggesting that the PITX1/MTNR1A/CREB axis regulates PER2 expression (Fig. 3). PER2 levels can affect peripheral organs by modulating clock-controlled genes, as it is one of the key components of the circadian clock gene (65). Taken together, MTNR1A expression is upregulated by PITX1 and hnRNPL at the transcriptional and post-transcriptional levels, respectively.

Although the daily rhythms of MTNR1A have been extensively demonstrated in the SCN, adrenal gland, mammary gland and liver, the diurnal change of MTNR1A in kidneys has been rarely studied. The daily changes of *MTNR1A*, PITX1, hnRNPL, nuclear enriched abundant transcript 1 (*NEAT1*) and phosphorylated-CREB (pCREB) were detected in renal tissue (26,66). The data indicated that *MTNR1A* and *NEAT1*

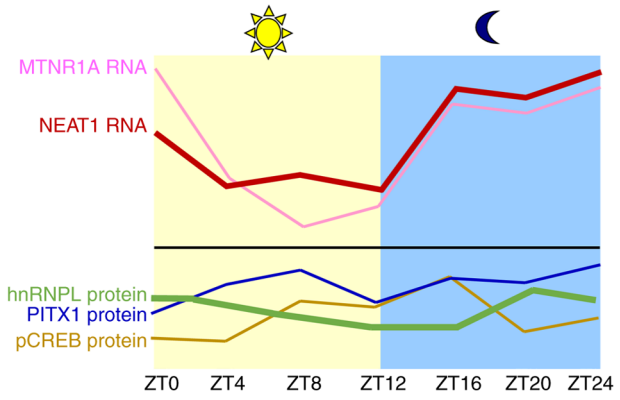

Figure 4. Schematic diagram illustrates the circadian rhythm of gene expression levels in the mouse kidney. The peaks in the diagram indicate maximum expression levels, and the dips indicate minimum expression levels, thus representing the period and amplitude of each gene's oscillation. The upper portion of the figure illustrates the patterns of *MTNR1A* mRNA (pink line) and *NEAT1* transcripts (red line). The lower portion shows the patterns of pCREB (orange line), PITX1 protein (blue line) and hnRNPL (green line). The thickness of the line is positively associated with the gene levels. The x-axis indicates Zeitgeber time (ZT). MTNR1A, melatonin receptor 1A; NEAT1, nuclear enriched abundant transcript 1; CREB, cAMP responsive element binding protein; pCREB, phosphorylated CREB; PITX1, pituitary homeobox-1; hnRNPL, heterogeneous nuclear ribonucleoprotein L.

expression demonstrated a higher amplitude compared with hnRNPL, PITX1 and pCREB proteins (Fig. 4). These findings suggest that *MTNR1A* and *NEAT1* RNAs may function as clock-controlled genes within the kidney. Furthermore, the similar pattern of period and amplitude observed for *MTNR1A* and *NEAT1* transcript levels suggests a correlation between NEAT1 and MTNR1A. Consistent with expectations, melatonin enhances NEAT1 expression in a manner dependent on the MTNR1A receptor in TECs (66).

Our data further demonstrated that *MTNR1A* expression decreases between ZT0 and ZT8, followed by a rapid increase between ZT12 and ZT16 (Fig. 4). Among the tested proteins, only pCREB displayed a clear diurnal rhythm, peaking at ZT16 (Fig. 4). Notably, pCREB levels negatively correlated with MTNR1A transcript levels between ZT4 and ZT12, suggesting that reduced *MTNR1A* expression may lead to diminished CREB activation. The detailed mechanisms by which PITX1 and hnRNPL regulate MTNR1A expression in TECs, depending on timing and genomic context, remain unclear.

The pathological lesions in MN include TECs' damage (67). The reason is abnormal glomerular permeability to proteins, which causes renal tubular cell dysfunction (68). Therefore, MTNR1A expression in TECs was investigated using an albumin-injury cell model and an experimental model of MN. The results indicated that albumin triggered downregulation of MTNR1A and PITX1 levels in the TEC cell line HK-2 and in MN kidneys. Mechanistic findings revealed low PITX1 expression in this albumin-induced TEC injury model, leading to reduced recruitment of PITX1 to the MTNR1A promoter (49). Notably, PITX1 levels decreased and associated with MTNR1A expression in clinical MN kidney (49). These results suggest a potential molecular mechanism of low MTNR1A levels in TEC underlying proteinuria damage.

6. Single nucleotide polymorphisms (SNPs) in MTNR1A

Previously, eight SNPs, namely rs216666, rs4862705, rs684769, rs117287777, rs6553010, rs1946977, rs7687823 and rs13140012, in the MTNR1A gene region were genotyped in 489 patients with type 1 diabetes (69). The authors evaluated the associations of these eight SNPs with the decline in renal function over a median follow-up period of 8 years (70). The results indicated that only the A allele of rs4862705 was observed at a higher frequency in patients with renal function decline compared with non-decliners (69). rs4862705 is located in 3' of MTNR1A gene and located in LOC105377596 gene. The two genes overlap, suggesting that rs4862705 affects LOC105377596 expression, then affecting MTNR1A transcription. This mechanism is similar with the X chromosome inactivation (XCI) process, two non-coding RNA X inactive specific transcript (Xist) and Xist antisense RNA transcribed in a mutually exclusive manner to mediated XCI in female cells (71,72). Further studies are necessary to confirm this molecular mechanism.

A recent study has identified the MTNR1A variant rs374152717 as a genetic determinant of idiopathic osteoporosis, a rare form of early-onset osteoporosis characterized by unexplained bone loss (73). Specifically, MTNR1A variant rs374152717, which disrupts the 5'consensus donor splice site in one allele, results in alternative splicing variants and subsequent partial translational deficiency (Fig. 3), leading to dysregulation of melatonin signaling (73). The mouse model of the rs374152717 variant and Mtnr1a$^{+/-}$ reproduced the low bone mass and hypercalciuria phenotype of young-adult patients with idiopathic osteoporosis (70). Collectively, the rs374152717 variant leads to reduced MTNR1A protein levels and decreased bone mass. This research establishes MTNR1A as a critical genetic factor in osteoporosis, offering new avenues for diagnosis, genetic counseling and therapeutic development.

A previous study indicated that MN mice treated with the MTNR1A antagonist luzindole exhibited a marked increase in proteinuria and hypercholesterolemia, along with a marked decrease in serum albumin (49). These results suggest that blocking MTNR1A receptor-mediated signaling worsened renal function in this experimental MN model. Consistent with this, decreased MTNR1A levels were observed in clinical MN specimens. Given that the MTNR1A variant rs374152717 reduces its expression (73), it warrants investigation whether this variant is present in clinical MN kidneys.

7. Exogenous melatonin treatment in MN

Elevated melatonin levels can attenuate environmental stress-induced damage through the regulation of complex interactions between immune cells, cytokines and signaling pathways (74). Exogenous melatonin exhibits pleiotropic therapeutic effects in various kidney diseases, including those related to hypertension, diabetes mellitus, acute kidney injury, CKD and MN (30,56). Taking MN as an example, the renoprotective mechanisms of exogenous melatonin include antioxidant, anti-apoptotic and anti-inflammatory effects (56). In MN mice treated with exogenous melatonin (MN-melatonin), elevated levels of CD19^{+} B cells were observed, while T cell levels remained unchanged.

Additionally, heme oxygenase-1 (HO-1) expression was higher in both glomerular and TECs in the MN-melatonin mice compared with MN mice (Fig. 3). Of note, the renoprotective effect of melatonin was reduced by treatment with a HO-1 inhibitor zinc protoporphyrin (ZnPP) in an experimental MN model (56). Although the role of elevated HO-1 in glomerular and TECs is unknown in experimental MN kidney, its mediated protective mechanisms in podocytes and TECs have been demonstrated in various mouse models (75). Induction of HO-1 against apoptosis activity in podocytes treated with high glucose has been observed and in diabetic kidneys (76). Moreover, HO-1 inhibits inflammation by suppressing pyroptosis in lipopolysaccharide (LPS)-exposed TECs (77). These results suggest that HO-1 expression protects podocytes and TECs against diabetic and LPS-induced conditions (77). Given that ZnPP inhibit both HO-1 and HO-2 (78), these results cannot definitively determine whether the protective effect in podocytes and TECs was due to the blockade of HO-1, HO-2, or both activities. Further studies should include the specific HO-1 target inhibitor.

The physiological conditions of the kidney can be modulated by endogenous or exogenous melatonin through the regulation of clock-controlled coding genes (79). However, there have been no studies indicating which long non-coding RNAs (lncRNAs) are clock-controlled and regulated by melatonin in the kidney. Recently, unpublished results by the authors demonstrated that exogenous melatonin upregulated clock-controlled lncRNAs, including nuclear enriched abundant transcript 1 (*NEAT1*), which is important for maintaining paraspeckles (66,80). The molecular mechanism discovered that melatonin enhances *NEAT1* transactivation by increasing the stabilization of BMAL1, which targets the NEAT1 promoter via the MTNR1A receptor (Fig. 3). Furthermore, melatonin enhances cell viability by increasing the occupancy of H3K27ac and H3K4me1 at the upstream regions of proliferation gene Ki-67 (81), counteracting albumin-induced injury to TECs. Collectively, these findings suggest that melatonin treatment ameliorates experimental MN through multiple pathways, including the elevation of HO-1 and *NEAT1* levels in TECs and the augmentation of $CD19^+$ B cells.

8. Exploring the clinical utility of melatonin in kidney disease management

The promising use of exogenous melatonin has been demonstrated in preclinical studies across various experimental models, including adriamycin-induced nephropathy, 5/6 nephrectomy, unilateral ureteral obstruction, spontaneously hypertensive rats and MN (49,82). Moreover, increasing evidence suggests a correlation between melatonin levels and renal function (83). Abnormalities in serum melatonin amplitude and rhythm are associated with the severity of CKD in patients (83). Nighttime urinary 6-sulphatoxymelatonin (6-SMT) levels, a major metabolite of melatonin, were found to be lower in patients with stage 5 CKD compared with those in other CKD stages (84). Decreased urinary 6-SMT levels were positively associated with renal function parameters (84). These findings support the hypothesis that exogenous melatonin could potentially slow CKD progression and benefit other kidney diseases in clinical practice. A small clinical trial (NCT04336566) evaluated the impact of a 5 mg daily dose of melatonin on renal function in CKD, but the results are pending. While melatonin itself is not directly metabolized by the kidneys, its metabolites are renally excreted. Therefore, CKD patients with renal insufficiency or those on dialysis should use melatonin at a low recommended daily dose of 0.5-3 mg.

The absence of published results on ClinicalTrials.gov concerning exogenous melatonin use in non-malignant kidney disease treatment can be attributed to several factors. Primarily, melatonin's natural and largely unpatentable nature makes it difficult to attract industry sponsorship for extensive, high-quality trials in kidney disease. Furthermore, the typically slow progression of CKD contributes to the time-consuming and costly nature of such studies. Consequently, the development of novel drugs aimed at enhancing melatonin expression or melatonin receptor levels represents a promising new direction for melatonin signaling therapy.

Previous clinical studies have indicated that after a 12-week administration period, exogenous melatonin has beneficial effects on glycemic control, high-density lipoprotein cholesterol levels, and peroxisome proliferator-activated receptor gamma expression in patients with diabetic nephropathy (DN) (85). However, it did not affect other metabolic parameters related to renal functions. (85). It was hypothesized that the lack of improvement in renal function with exogenous melatonin treatment may be attributed to the downregulation of melatonin receptors in DN. Therefore, combined melatonin and elevated MTNR1A drug treatment could be beneficial for these patients. Hence, drugs that enhance MTNR1A activity or expression may also enhance melatonin's renoprotective functions.

9. Conclusion

The melatonin signaling pathway is a functionally conserved and broad-spectrum physiological modulator found in vertebrates. In the present study, the expression levels of melatonin synthesis components and melatonin receptors in renal TEC were summarized. The highest expression of DDC and MTNR1A compared with other genes involved in the melatonin pathway in the kidney was demonstrated. Using experimental models of MN and albumin injury, reduced MTNR1A expression in renal TEC was further identified, leading to upregulation of PER2 gene expression within the MTNR1A/CREB axis. The molecular mechanism demonstrates that MTNR1A is upregulated by PITX1 in a transcriptional manner and by hnRNPL in a post-transcriptional manner in TECs. MTNR1A is reduced in TEC and correlated with PITX1 in clinical MN samples. Exogenous melatonin treatment alleviated the severity of experimental MN by upregulating $CD19^+$ B cells and HO-1 expression in both glomerular and TECs. Moreover, melatonin enhances cell viability by increasing NEAT1 transactivation through MTNR1A receptor and its mediated Ki-67 expression in response to albumin-induced injury in TECs. These results suggest that low MTNR1A in TECs worsens renal function in experimental MN models. However, the clinical relevance of decreased MTNR1A in MN progression should be investigated in the future.

10 Future directions

Primary MN is an autoimmune glomerular disease typically caused by circulating autoantibodies targeting podocytes, predominantly anti-phospholipase A2 receptor autoantibodies (70-75%) (86). After immune complexes form and deposit, complement activation ensues, leading to podocyte damage and alteration of the glomerular basement membrane. The toxic effects of filtered proteinuria on renal TECs exacerbate injury and promote TEC death, contributing to tubular atrophy and interstitial fibrosis, which drive progression of CKD toward ESRD (87). Consistent with this notion, ~1/3 of patients with MN will progress to ESRD within 10 years (88,89). However, the current therapeutic approach for MN patients involves the use of renin-angiotensin system blockers and immunosuppressive agents targeting activated B cells, effector T cells, complement activation and cytokine production, without a specific focus on treating TECs (90). New drugs that specifically target TECs to counteract proteinuria-induced fibrosis in MN should be explored. Evidence suggests that MNTR1A levels in TECs are associated with MN severity, indicating that MTNR1A could be a potential therapeutic target for treating CKD progression. Therefore, exploring drugs that enhance MTNR1A expression in TECs could leverage endogenous melatonin signaling to improve renal function in patients with MN and CKD.

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Availability of data and materials

Not applicable.

Authors' contributions

YSH and CCW designed and wrote the review. SMK, KCL and AC revised and provided comments during all stages of writing the manuscript. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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