

The reno-pineal axis: A novel role for melatonin

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ABSTRACT

The pineal gland is a tiny endocrine gland whose physiologic role has been the focus of much research and much more speculation over the past century. This mini-review discusses recent findings which correlate melatonin and renal physiology, and postulates the presence of a “reno-pineal axis.” Drawing lessons from comparative endocrinology, while quoting human data, it advocates the need to study the “reno-pineal axis” in greater detail.

Key words: Kidney, melatonin, pineal, renal endocrinology, reno-pineal axis

INTRODUCTION

The pineal gland is a small, single endocrine organ located near the center of the brain. Derived from the diencephalon, it shares its origin with the lateral eyes and the hypothalamus. This common embryological source allows these organs to work together as a photoneuroendocrine system which follows a distinct endogenous, rhythmic, and circadian pattern.^[1]

L-tryptophan, an essential amino acid, is converted to serotonin with the help of the enzymes tryptophan hydroxylase and 5-hydroxytryptophan decarboxylase. Serotonin levels increase on exposure to light and decrease during the dark because it is converted to melatonin during the dark phase. Formation of melatonin occurs mainly not only in the pineal gland, but also in the retina, and is catalyzed by *N*-acetyltransferase and hydroxyindole-*O*-methyl transferase enzymes. The hormone is secreted directly into the bloodstream and cerebrospinal fluid upon synthesis. Physiologically, melatonin secretion increases about 2 hours after bed time and decreases by morning. It is inactivated in the liver to 6-hydroxyl melatonin, which

is excreted into urine and feces as sulfate and glucuronide conjugates. A small percentage (2–3%) is excreted as melatonin in the urine.^[1]

In the newborn, it takes 9–12 weeks for melatonin secretion to begin. Levels reach their highest peak at 1–3 years and then fall at puberty, decreasing gradually thereafter.

Though substantial inter-individual variability in melatonin levels is noted, the age-related declining trend is observed consistently. This may be because of greater volume of distribution due to increasing body mass in childhood and early adult life, decreased production because of pineal calcification, and reduced sympathetic innervations of the pineal gland, without which melatonin cannot be secreted.^[1,2]

Melatonin reaches every cell of the body due to its highly lipophilic nature. The receptors MT1 and MT2 are G protein-coupled receptors which are present in many body tissues, including the pituitary hormone and kidney.^[2]

RENAL EFFECTS OF MELATONIN

While the physiologic functions of melatonin related to regulation of sleep, reproduction, and thermoregulation have been documented for long, its effects on renal function are being discovered only now.^[3,4] That melatonin acts upon the kidney has been proven by numerous experimental and human data. Melatonin seems to work through multiple pathways: as an antioxidant, as an apoptosis modulator, and as a circadian modulator of vascular function.

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This review focuses only on the renal effects and correlations of melatonin, based on animal and human data, and tries to build the case for the presence of a reno-pineal axis. It does not try to discuss other novel aspects of melatonin physiology, which have been covered elsewhere.^[4]

EFFECTS ON REACTIVE OXYGEN SPECIES

Development of diabetic nephropathy has been found to be linked with decrease in melatonin-induced reactive oxygen species (ROS) generation and mitochondrial complex-3 (MC-3) activity. Melatonin may contribute to the regulation of mitochondrial complexes, and its deficiency may lead to differential regulation of the MC-1 and MC-3 proteins in the renal mitochondria.^[5] This in turn may lead to an imbalance in ROS generation. This is a potential pathway for the reno-pineal axis. This hypothesis is supported by findings from various researchers who have found beneficial effects of melatonin on renal injury caused by FK506, colistin radiocontrast, and lead, amongst others.^[6-9] FK506 is a melatonin agonist which provided a suitable animal model to study the effects of melatonin on oxidative stress.

The antioxidant effect of melatonin is not limited to the kidney. The hormone has been found to increase the gene expression for antioxidant enzyme in the rat brain, improve insulin sensitivity, and have multiple beneficial effects in metabolic syndrome.^[4,10]

EFFECTS ON CELL PROLIFERATION

Melatonin has been proposed to have beneficial effects on cell proliferation by reducing the apoptosis of healthy cells, while enhancing the apoptosis of malignant cells. This aspect of pineal physiology has been studied in the kidney as well. Studies have been done on renal carcinoma cells, which show that melatonin sensitizes these cells to apoptosis.^[11,12] On the other hand, it markedly slows the progression of renal damage in rats with renal mass reduction (surgical ablation).^[13] Melatonin has been shown to attenuate oxaliplatin-induced apoptosis in cancer cells by inhibiting glutathione (GSH) depletion and Mcl-1 downregulation.^[12]

EFFECTS ON VASCULAR FLOW

These effects are linked to melatonin's actions upon the vascular bed. Melatonin levels have been shown to be inversely related with ambient blood pressure. This was observed using urinary melatonin levels in a cohort of young women.^[14] Similar findings were noted in non-dipper hypertensive men and women, who had low or nocturnal secretion of the hormone.^[15] These observations translated into an interventional trial in which prolonged melatonin administration decreased nocturnal

blood pressure in women.^[16]

While this may appear simplistic, a recent study has been found to have differential effect on various vascular beds. It reduces renal blood flow, which may impact the so called reno-pineal interaction.^[17]

A therapeutic role for melatonin has been suggested, based on its beneficial role in ischemia reperfusion injury in renal grafts.^[18]

EFFECT ON TUBULAR FUNCTION

Most renal functions, including glomerular filtration rate, urine production, and solute excretion, exhibit circadian changes. There is an increase in the concentration of urine during the nocturnal period, which may be mediated by melatonin, i.e. the pineal gland. In healthy humans, nocturnal excretion rates of sodium, potassium, chloride, and urate are only 50% of the rates observed during the light period,^[19] whereas phosphate reabsorption at night exceeds that during the day.^[20] Further, administration of melatonin to hamsters decreases urinary sodium and potassium concentrations as well as urine osmolality.^[21] MR are predominantly localized in the proximal tubular segments. This localization suggests that melatonin probably influences renal function through regulation of proximal tubular function.

Melatonin has been found to reduce renal blood flow, which may in some way explain the effects on renal physiology.^[22]

EFFECT ON NEPHROLITHIASIS

In tandem, the above mentioned effects may have an impact on the occurrence of renal colic in patients predisposed to the condition. A retrospective study of 1481 Iranian patients with renal colic revealed a higher frequency in the middle of the lunar month (days 14–17) and the lowest frequency of hospital admission during the extreme days of the lunar month.^[23]

It has been proposed that the predisposition to renal calculi is linked with abnormalities of the melatonin receptor 1A (*MTNR 1A*) gene, which is associated with calcium metabolism.^[24]

Melatonin also has a potential therapeutic role in nephrolithiasis, as it protects against shock wave associated renal damage during lithotripsy.^[25]

EFFECTS ON PROTEINURIA

The renal spectrum of the reno-pineal axis encompasses interstitial, tubular, as well as glomerular function. Human

studies have shown impairment of endogenous circadian melatonin secretion in chronic kidney disease (CKD).^[24] While the exact cause and effect relationship is unclear, the impairment is related to the degree of CKD and worsens with progression of CKD.^[26]

Animal studies have demonstrated the utility of melatonin in reducing inflammation and proteinuria, as well as retarding progression of renal failure. While this has been shown only in surgically induced renal ablation, in rat models, it holds a promise for therapeutic use of melatonin in CKD in humans.^[13] The drug may have a role in managing sleep disturbances seen in patients on chronic dialysis therapy.

PHARMACOLOGIC STUDIES

Few pharmacologic studies have been performed using melatonin. This is surprising, considering the fact that it is easily available, easy to administer, and is an economical drug with a wide array of potential activity. However, the lack of patent protection discourages pharmaceutical majors from funding research on melatonin.

CONCLUSION

The pineal gland seems to be linked with renal physiology through the pleiotropic actions of melatonin. The exact mechanism of the reno-pineal axis is yet to be delineated. However, association of melatonin with ROS, renal cell apoptosis, renal cell mass, glomerular function, tubular function, as well as vascular function indicates that the reno-pineal link is a multifaceted one. More work needs to be done to elucidate the physiologic and biochemical details of the reno-pineal axis so as to harness the therapeutic potential of this hormone.

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