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Melatonin and kidney; a narrative review on the renoprotective efficacy of melatonin in various renal diseases

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Abstract

Melatonin, a synthetic product of the vertebrate pineal gland as well as of other select organs, is critical for the regulation of circadian and seasonal alterations in various aspects of physiology and neuroendocrine functions. Melatonin was shown to have notably wide actions including anti-inflammatory activity due to its high antioxidant potential as a powerful free radical scavenger. Melatonin reduces macromolecular damage in all organs through its ability to scavenge toxic free radicals such as renal tubular cell injury. Some other disorders related to chronic kidney diseases treatable by melatonin is sleep–wake rhythm disturbances between different dialysis groups as well as in high blood pressure in diabetic nephropathy patients. As age advances, the nocturnal production of melatonin decreases in animals of various species, as well as in human. The adrenal of elderly people is hypersensitive to adrenocorticotropic hormone. On the other hand, midnight corticoid balances are grew up in old ages, so the effects of melatonin on the secretion of corticoids have been indicated that modification of corticoid-related phenomena can clarify considerably melatonin's apparent antiaging and other valuable actions. Melatonin can also play a vital role in renal protection against dangerous free radicals which can be harmful for kidney function followed by renal tissue destruction.

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Introduction

In pineal gland, the rhythmic release of melatonin is modulated by norepinephrine (NE) secreted from the sympathetic nerve fibers. These fibers constitute the last part of multisynaptic way connecting the gland with suprachiasmatic nucleus (SCN) and indirectly with the retina. Several studies performed through the last years of the 20th century on the pineal gland of rat model allow the scientists to prepare a detailed of adrenergic regulation of melatonin exertion in these species (1). Melatonin was found to be a free radical scavenger less than 10 years ago. Further it has the proficiency to neutralize a number of free radicals and reactive oxygen and nitrogen species, to stimulate numerous antioxidative enzymes such as superoxide dismutase, glutathione peroxidase and glutathione reductase which increase its efficacy as an antioxidant (2). Also, melatonin neutralizes hydrogen peroxide, singlet oxygen and has been mostly used as a protective agent against a wide variety of processes and agents involved in damage tissues via free radical mechanisms (3). It appears from the aforementioned investigations that numerous investigations have been conducted tissue protective effects such as heart and kidney, however there were many researches about tissue damaging, few of them focused on renal injury treatable by melatonin. So it is necessary to do deep researches on effects of melatonin on kidney disorders and their consequences.

Core tip

Melatonin, the main pineal hormone is identified to synchronize circadian rhythm and to regulate immune system activities and recently reported as a scavenger of a number of reactive nitrogen species and reactive oxygen in vitro and in vivo.

While pineal hormone, melatonin, plays a major role in circadian sleep-wake rhythm, individuals with chronic renal failure, particularly those who are on regular hemodialysis, frequently suffer from sleep disturbances. The therapeutic profit of melatonin therapy in sleep disorders linked to chronic kidney disease has been proved in some experimental examinations. Additionally, this mater and the positive effects of melatonin on blood

pressure alterations in diabetic sufferers and the protection of melatonin in oxidative stress and inflammation in renal disorders are explored.

Materials and Methods

In this review a variety of sources have been used by searching through PubMed/Medline, Scopus, EMBASE, EBSCO and directory of open access journals (DOAJ). The search was conducted, using combination of the following key words and, or their equivalents; free radicals, reactive oxygen species, melatonin, diabetes mellitus, antioxidants, oxidative stress, renoprotective effects and renal disease.

Antioxidant activity of melatonin

Antioxidants have attracted a great deal of attention as potential agents for treatment of a wide variety of diseases (4-6). The discovery of melatonin as a direct free radical scavenger and as an indirect antioxidant through stimulating antioxidant enzymes has considerably improved attention in the use of this agent in the tentative arranging. Its possible function in humans is supported by its very low toxicity and its availability in a pure form and the fact that it is inexpensive make it easy to use (2,3).

Melatonin seems to have function by a number of means to diminish oxidative stress. Thus, the tentative indication defend its acts as a direct free radical scavenger and also an indirect antioxidant which can stimulate antioxidant enzymes, because these enzymes provide a major defense mechanism against free radical injury either by metabolizing them to less reactive species or to non-toxic byproducts. The important antioxidative enzymes that have been detected relative to melatonin are the superoxide dismutase, glutathione reductase catalase, glucose-6-phosphate dehydrogenase and glutathione peroxidase (2,7).

Renoprotective effects of melatonin

Kidney is an organ with vital value. It has a crucial and physiological function in homeostasis and metabolism. Some drugs disturb renal perfusion and induce loss of filtration capacity. Others straight injure vascular, tubular, glomerular and interstitial cells meanwhile melatonin and its metabolites have dominant anti-inflammatory specifications and have proven to be highly effective in a variety of illnesses linked to oxidative stress and inflammation in experimental animals. It has been effectively used in various nephrotoxic models (8).

Melatonin has been shown to possess anti-inflammatory effects, among a number of acts. For example it can decrease tissue damage during inflammatory reactions by a number of means. Thus melatonin reduces macromolecular damage in all organs through its ability to scavenge toxic free radicals (2-7).

Melatonin has been found to be protective against glycerol-induced renal failure because of its antioxidant effect also reduced interstitial renal inflammation and recovered hypertension in unexpectedly hypertensive rats (8).

Role of melatonin in treatment of acute kidney injury

Aminoglycoside antibiotics consisting gentamicin are used in the treatment of some infective agents like gram-negatives. A main difficulty of these drugs is nephrotoxicity. Frequent courses of aminoglycoside therapy and persistently high peak quantities expose kidneys to high concentrations of the drug. This may result in accumulation of aminoglycosides in the renal cortex predisposing the patient to acute kidney injury (AKI) (9).

Several studies have shown that gentamicin enhances the generation of ROS metabolites in renal cortical mitochondria (10). In vivo studies have shown the protective impact of hydroxyl radical scavengers and/or iron chelators in various models of tissue injury. Therefore, antioxidants are expected to decrease renal injury associated with oxidative challenges (7,10). As regard its protective effects, melatonin was found to protect tissues against oxidative damage generated by a variety of toxic agents including aminoglycoside antibiotics and has been successfully used in various nephrotoxic models. Melatonin protects the heart and lungs from oxidative stress under intermittent hypobaric hypoxia in rats (7,9,10).

In our previous study entitled "ameliorative impact of melatonin against contrast media induced kidney tubular cell damage", we investigated melatonin as a potent-free radical scavenger. Our aim was to test whether melatonin would be useful in contrast media nephrotoxicity. In this regard in an experimental study 40 adult male Wistar rats were distributed into four groups including; control group, contrast media group, contrast media and melatonin and contrast media plus melatonin pretreatment group. The blood creatinine and BUN as well as the histological changes were assessed to detect the intensity of kidney damage such as degeneration, vacuolization of tubular renal cells, tubular lumen dilatation and existence of debris in the lumens. Our results showed significant increase in creatinine, BUN and renal injury score in contrast media group ($P<0.05$). Melatonin prevented and reversed the damage generated by contrast media ($P<0.05$). Furthermore pretreatment and melatonin reduced the renal injury induced by contrast media ($P<0.05$). At the end of study we established that melatonin was an effective drug to prevent contrast-induced renal injury. Hence, it is evident that the administration of melatonin in patients who are planning to use contrast media agents can be helpful (10).

Not only renal tubular cell injury can be reduced by melatonin but also it can be applied in renal replacement therapy in end-stage renal disease (ESRD). Another problem in patients involved in kidney disease is sleep–wake rhythm disturbances between different dialysis groups which melatonin might be beneficial (11).

Patients with chronic renal failure including those enduring hemodialysis have disrupted sleep-wake pattern. In large part, this is due to an abnormal circadian cycle of melatonin. Individuals undergoing regular peritoneal dialysis or nocturnal hemodialysis have better sleep profile compared to those on daytime regular dialysis. Studies have conclusively been shown that exogenous melatonin improves sleep-wake cycle in daytime hemodialysis patients (12). On the other hand, patients with chronic renal failure, particularly those who are on hemodialysis suffer from sleep disturbances re-

peatedly. Hence the beneficial effect of melatonin on blood pressure alterations in chronic renal failure states and the protective effect of melatonin in oxidative stress and inflammation in renal disorders is essential (13).

In some studies, there are differences between continuous ambulatory peritoneal dialysis (CAPD) and automated peritoneal dialysis (APD) because on one hand, an absence of the nocturnal raise in melatonin level in daytime hemodialysis patients has been described earlier and on the other hand there are insufficient comparative data on sleep–wake rhythm instabilities between different dialysis groups. However, it has been described that sleep disorders have more impact on hemodialysis patients than peritoneal dialysis. Another study showed an improvement of sleep apnea when moving from CAPD to APD (14).

ESRD is associated with an strengthened prevalence of sleep disorders, furthermore, the wake-sleep circadian rhythm, stating cycles of low and high sleep propensity, may be negatively influenced in this individuals group due to the etiology of ESRD and the hemodialysis process, causing nocturnal insomnia and daytime sleepiness (11,14).

Melatonin and diabetes

Diabetes is another high-ranking reason for kidney damage. One of the kidney diseases resulted from diabetes is diabetic nephropathy. People with diabetes and kidney disease at the same time have worse condition than people with kidney disease alone. This is because individuals with diabetes tend to have other long-standing medical conditions, such as high blood pressure, high cholesterol, and blood vessel disorders. Lack of melatonin has effects on insulin levels and the stimulation of blood glucose in rats and can cause a noticeable decline of insulin secretion by rat pancreatic islets. In postmenopausal women, the oral taking of 1 mg of melatonin reduced glucose tolerance and insulin sensitivity. Also melatonin administration reduced visceral fat, plasma insulin and IGF-1 levels at middle age rats. Additionally long-term treatment with melatonin reduced hyperinsulinemia, hyperleptinemia, hypertriglyceridemia, and restored hepatic delta-5 desaturase activity in type 2 diabetic rats (15). The use of melatonin in normal rats led to significant decrease in serum leptin levels compared to those of control animals (16). Melatonin significantly augmented the level of total and free cholesterol and high-density lipoprotein cholesterol in rat blood. Supplementation of the diet with melatonin resulted in a raise of atherosclerotic lesions surface in the proximal aorta of hypercholesterolemic mice and raised the ability to ex vivo oxidation of atherogenic lipoproteins extracted from the plasma during the fasting period. However, there are reports on the inhibitory influence of high dosages of melatonin on the oxidation of low density lipids in some clinical studies (15,16).

Melatonin and aging

Sleep is a biologic process, and its structure, quality and duration, are varied in many conditions such as aging. The precise contribution of aging per se or of the interaction between age and multiple factors for instance biological, socio-economical and psychological factors to sleep changes is difficult to disentangle. Sleep quality, structure and duration have different dynamics during aging and related diseases, however common patterns can be recognized both in healthy aging and in individuals with intrinsic sleep disorders.

Melatonin levels decline with age in humans, and the nocturnal melatonin surge is virtually completely lost. Because of the close reciprocal relation of melatonin and corticoids, this deficiency of melatonin rhythmicity may be accountable for the pituitary/adrenal axis disinhibition that has been described as a characteristic of aging (17). The adrenals of elderly humans are apparently hypersensitive to adrenocorticotropic hormone and midnight corticoid balances are obviously raised in old age. The effects of melatonin on both the release of corticoids and their influences, the pathogenic conditioning influence of corticoid excess, and the phasic prohibitory impact of melatonin on the pituitary/adrenal axis have been designated that modification of corticoid-related phenomena can clarify considerably melatonin's apparent antiaging and other beneficial actions (17).

Clinical point of view

There is a large volume of published investigations defining a nephrology view point of melatonin. In this regard Patschan et al have proposed that endothelial progenitor cells (EPCs) protect the kidney from acute ischemic injury. They examined whether pre-therapy of murine "early outgrowth" EPCs with the melatonin hormone increases the cells' renoprotective influences in acute ischemic renal failure. In this investigation animals injecting with untreated cells advanced severe renal failure and eEPC pretreatment with melatonin dramatically improved renoprotective actions of the cells. These results were wholly preserved after cell pretreatment with melatonin and the MT-1/-2 antagonist luzindole. In vitro examination showed that melatonin diminished the amount of tumor growth factor-β-induced eEPC apoptosis/necrosis. Secretion of vascular endothelial growth factor by the cells was significantly stimulated by the hormone. In addition, migratory activity of eEPCs was increased by melatonin and supernatant from melatonin-treated eEPCs stimulated migration of cultured mature endothelial cells. In consequence of this, melatonin was known as a new agonist of eEPCs in acute ischemic kidney injury (18).

In an another study, Cheng et al researched the effects of melatonin therapy on chronic kidney disease followed by hypertension. Nitric oxide (NO) deficiency happens in humans and animals with chronic renal failure. N(G)-nitro-l-arginine methyl ester (L-NAME), an inhibitor of NO synthase, provoked kidney damage in the adult spontaneously hypertensive rat (SHR). L-NAME induced an increase of ADMA (asymmetric dimethylarginine) and a decrease of arginine-to-ADMA ratio in the SHR kidney. In this study they indicated that hypertension and nephrosclerosis in young SHRs exacerbated by L-NAME could be prevented by melatonin therapy. In addition, melatonin decreased renal ADMA concentrations, increased renal arginine-to-ADMA ratio, and remade NO generation in L-NAME-treated young SHRs. Also, melatonin diminished

the degree of oxidative damaged (19).

A series of cases reported that melatonin improved platelet counts in patients with idiopathic thrombocytopenic purpura. Melatonin was also found to be useful in cisplatin-and cyclosporine- induced acute kidney damage, cardiotoxicity caused by doxorubicin, and a number of other drug-induced diseases (20).

Conclusion

Consequently, melatonin is one of the most powerful antioxidant secreted by pineal gland because of its high ability in lowering oxidative damage and strong free radical scavenging property. Melatonin antioxidative functions such as synergistic actions with classic antioxidants, stimulation of the synthesis of the important intracellular antioxidant GSH, its unique intracellular distribution, the fact that second and third generation metabolites of melatonin are also effective scavengers, its ability to reduce free radical generation at the mitochondrial level, as well as yet undefined actions make it a unique drug agent for prevention and treatment of renal damage as well as other oxidative stress induced diseases. It is clear that while melatonin is protective against oxidative stress, the mechanisms that it attains this high level of protection requires more extensive investigations. Conclusions drawn from this work include the high antioxidant ability of melatonin and its boosting role in protecting kidney against tissue damaging during inflammatory reactions. Furthermore its utility in treatment of some crucial side effects of kidney damage such as sleep-wake disturbances in chronic kidney diseases patients is also important. Obviously, due to the very large number of reports that have appeared relate to the favorable functions of melatonin under high oxidative stress conditions, all the publications could not be cited in the current review. Rather, a few conditions where the clinical utility of melatonin could be more noticeable and where the amount of experimental data were abundant were selected for inclusion.

Authors' contribution

All authors contributed to design of the research. SK prepared the primary draft. PN and MRA search the data and conducted primary editing. MRK edited the final manuscript.

Conflicts of interest

The authors declared no competing interests.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, and duplicate publication) have been completely observed by the authors.

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