Review

Current Urology

Curr Urol 2014;8:113–118
DOI: 10.1159/000365701

Received: January 12, 2015
Accepted: February 20, 2015
Published online: September 4, 2015

Melatonin and Its Role in Lower Urinary Tract Function: An Article Review

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Key Words

Melatonin • Bladder dysfunction • Inflammation • Antioxidant • Aging

Abstract

This article reviewed the results of studies done on animals that assessed effects of melatonin on bladder function. Melatonin does not change strip relaxation on its own. However, pretreatment with melatonin decreases contractile responses induced by phenylephrine, acetylcholine, bethanechol and KCl in a dose-dependent manner. The contractile responses induced by the direct calcium channel openers are significantly decreased by melatonin pretreatment. It also binds to Ca^{2+}-activated calmodulin, and prevents it from activating myosin light-chain kinase. It may have direct effects on ion channels which are responsible for regulating bladder contraction. Its other mode of action on bladder occurs via the brain $GABA_A$ receptor. Melatonin is an antioxidant. In bladder, treatment with melatonin prevents elevations in malondialdehyde levels, reverses changes in glutathione levels, and decreases myeloperoxidase levels compared with oxidative injury. It can normalize age induced bladder dysfunction through its antioxidant effects, inhibiting smooth muscle contractility directly and restoring impaired contractility via normalization of Ca^{2+} handling and sensitizations pathways. It attenuates the severity of cystitis and inflammation. Mast cell proliferation and activation are increased in cystitis, but decrease by melatonin treatment. Also, there is a decrease in expression levels of pro-inflammatory cytokines after melatonin treatment.

Introduction

Melatonin (N-acetyl-5-methoxytryptamine) is the major neurohormone secreted during the dark hours at night by the vertebrate pineal gland. After its formation, melatonin is released into the capillaries, and even in higher concentrations, into the cerebrospinal fluid and then spreads to most body tissues [1].

Generally, melatonin, which is the main product of the pineal gland, exerts many of its physiological actions through interaction with the membrane receptors MT1 and MT2 and intracellular proteins such as quinine reductase 2, calmodulin, calreticulin, and tubulin. Its receptors are found in the bladder as well as the prostate [2].

Melatonin may have two different effects on the vasculature, with vasoconstriction through MT1 and vasodilation through MT2 [3]. It decreases the contraction of the small and large intestines in rats, whereas it causes

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contraction of the colonic smooth muscle from guinea pig [3, 4]. It has the ability to vasoconstrict rat caudal and cerebral arteries, and to relax porcine arterial smooth muscle [5, 6].

In the current review article, we reviewed the results of studies that have been done on animals, and in which they assessed the effects of melatonin on bladder function. We performed a search of the English literature through PubMed. The key words used were "bladder" and "melatonin". Our data and perspective are provided for consideration of the future direction of research.

Results

Smooth Muscle Tone Adjustment

Melatonin is shown to be involved in a variety of physiological actions, and to adjust smooth muscle tone in different tissues. In the urinary tract, both acetylcholine and KCl can increase the myogenic activity of bladder strips. It does not change strip relaxation and has been shown to have a little effect on the contractility on its own. However, pretreatment with melatonin decreases the contractile responses induced by phenylephrine dose-dependently. Melatonin also attenuates the peak amplitude in acetylcholine-, bethanechol- and KCl-induced contraction in a concentration dependent manner [7]. Interestingly, the inhibitory effects of melatonin on contractions are not reversible with melatonin-receptor antagonists [8]. It suggests that melatonin inhibits bladder contraction by the modulation of intracellular proteins directly.

Although as stated previously melatonin has little direct effect on muscle relaxation, it markedly potentiates the block produced by succinylcholine, implying its function as a calcium-channel blocker [9]. Many reports suggest that it has inhibitory effect on rat ileal smooth muscle, where Ca-channels seem to be necessary for inducing the inhibition [10]. Moreover, it potentiates calcium channel antagonist-induced relaxation. However, potassium channel blockers do not change melatonin activity. Furthermore, melatonin, when given prior to calcium channel openers, decreases contractile responses to a great extent [8].

Another possible mechanism by which melatonin can induce bladder inhibition may be via its interaction with calmodulin. It is shown, in other organs, that melatonin has the ability to attach to Ca^{2+}-activated calmodulin with high affinity; the net effect will be its prevention from activating myosin light-chain kinase, which in turn will cause a decreased contractile response [11, 12]. Melatonin might have direct effects on other ion channels involved in regulating bladder contraction or changing membrane potentials which in turn affects other ion channels [11].

Melatonin has central effects on bladder function as well. Melatonin reinforces the action of the central nervous system GABAergic system [13–18]. Bicuculline, a $GABA_A$ antagonist which competes with $GABA_A$ receptor and increases the micturition reflex [19], has no significant change in bladder capacity and induces a significant increase in bladder pressure only at high doses [20]. Intracerebroventricular melatonin administration increases bladder capacity dose dependently, although it causes no significant difference in bladder contraction pressure. Bicuculline can inhibit melatonin induced increases in bladder capacity [20]. It indicates that one of melatonin actions on bladder occurs via the brain $GABA_A$ receptor, especially the GABA binding site, as direct melatonin administration to the cerebral ventricle excludes its action at the peripheral organ. Thus, melatonin is believed to suppress the micturition reflex by reinforcing brain GABAergic activity [20].

Oxidative Pathway

Free oxygen radicals have been referred to as a major cause of destruction and damage to cell membranes through lipid peroxidation. Lipid peroxidation involves degradation of polyunsaturated fatty acids of the cellular membranes. The process subsequently will result in disruption of membrane integrity. It will then lead to alterations in membrane permeability and also to increased and facilitated protein degradation, and these will eventually lead to cell lysis [21].

Melatonin is a potent free radical scavenger and antioxidant [22]. Malondialdehyde or glutathione are considered as an index of lipid peroxidation and an important part of intracellular protective mechanism against a variety of stimuli including oxidative stress [23].

In the bladder, melatonin has no effect on malondialdehyde and glutathione levels under normal circumstances; however, after oxidative damage, bladder malondialdehyde levels tend to be much higher than normal; In *in vitro* and *in vivo* experiments, melatonin has been demonstrated to have a protective effect on tissues against damage caused by a number of free radical generating agents and processes (i.e. lipopolysaccharide, kainic acid, Fenton reagents, potassium cyanide, L-cystein, excessive exercise, ischemia-reperfusion and radiation) [24–30]. The process involves reduction in lipid

peroxidation, and scavenging the hydroxyl radical, a potentially strong initiator of lipid peroxidation, and also the peroxyl radical, which enhances lipid peroxidation in other organs [24, 25, 31]. In another process, melatonin prevents catalase inactivation by scavenging hydrochlorous acid [32]. Moreover, peroxynitrite is shown to be another molecule undergoing the scavenging effect of melatonin [33]. Treatment with melatonin before and/or after oxidative injury prevents elevations in malondialdehyde levels of bladder [34–36].

Reduced glutathione, an intracellular free radical scavenging molecule, is considered as the main component of the endogenous non-protein sulfhydryl pool [23, 37]. The exposed sulfhydryl group on these molecules enables them to protect cells by binding to a variety of potentially damaging free radicals and metabolites [38]. By maintaining the concentration of reduced glutathione, glutathione peroxidase is a critical antioxidant enzyme. Melatonin facilitates this endogenous enzyme's activity by removing hydrogen peroxide [39]. Although melatonin treatment in the rats with oxidative injury reverses the changes in glutathione levels of bladder, whether or not melatonin has a direct effect specifically on bladder via glutathione activity stimulation is yet to be further studied [35, 36, 40].

Myeloperoxidase activity is an indicator of tissue neutrophil infiltration. Neutrophil migration and activation is accompanied by the production of radical oxygen metabolites (ROM) and release of various cytotoxic proteins (e.g. proteases, myeloperoxidase and lactoferrin) which induce cellular and tissue injury. Marked myeloperoxidase activity in bladders after oxidative injury indicates that sequestered neutrophils are the main source of ROMs. Melatonin treatment decreases myeloperoxidase levels compared with oxidative injury, however, melatonin treatment in the absence of oxidative damage has no significant effect on the myeloperoxidase activity of the bladder [36].

In normal circumstances, nitric oxide (NO) produced by constitutive nitric oxide synthase (NOS) has inhibitory effects on the detrusor. It also inhibits afferent nerve activity. On the other hand, very high concentrations of NO produced by iNOS is not well tolerated and can be cytotoxic and neurotoxic [41, 42]. Chronic treatment with melatonin increases nNOS expression and decreases iNOS expression in bladder tissue. This is another feature suggesting that melatonin may have protective effects on a chronically ischemic bladder through its free radical scavenging and antioxidative properties [36].

Nuclear erythroid 2-related factor 2 (Nrf2) is a transcription factor. It has a role in modification and regulation of oxidative agents and processes. It performs its regulatory role through the antioxidant response element found in the promoter region of many cytoprotective genes. Normally, Nrf2 is sequestered in the cytoplasm with an actin binding protein kelch-like ECH associated protein 1 (Keap1). Upon its activation by various processes, Nrf2 is released from Keap1, and moves into the nucleus to stimulate gene transcription [43]. The result is the upregulation of some antioxidant enzymes such as glutathione-s-transferases and superoxide dismutase, as well as redox sensitive enzymes, NADPH: quinone oxidoreductase-1, and heme oxygenase-1 (HO-1) [44]. It has been reported that Nrf2 plays an important role in modulating acute inflammatory responses by inhibiting nuclear factor-kappa B (NF-κB) activation, another molecule with similar properties [45]. Melatonin induces an increase in Nrf2 and NF-κB factors [46].

Aging

Most common abnormalities in voiding dysfunction in the elderly include obstruction, detrusor overactivity and impaired detrusor contraction [47] manifested as increased postvoid residual urine volume, decreased micturition interval and micturition volume. Senescent animals show spontaneous contractions during the filling phase, nonvoiding contractions, implying increased contractile activity in the detrusor muscle. However, it is shown that alterations in detrusor activity could also result from changes in the central nervous system [48].

Plasma melatonin has a circadian rhythm with high levels at night, and low levels during the day, reaching peak concentrations between 02:00 and 04:00 am. Longer nights are accompanied by a longer melatonin secretion [49]. Nocturnal melatonin production is not as efficient in the elderly population and many clinical trials showed that exogenous melatonin administration restores circadian disturbances [50]. It is known that aging is partly a result of ROMs accumulation [51]. Taking that into account, melatonin deficiency and/or its secretory disturbance may have a role in the increase in oxidative damage that occurs with aging [48].

Melatonin treatment restores the changes in residual volume and detrusor overactivity that develops by aging. It may exert its effect by maintaining circadian rhythm, improvement in physiological functions or by direct actions on the bladder. There has been shown to be a decrease in nocturnal urinary frequency after melatonin administration in those elderly patients with prior noc-

turia and bladder outlet obstruction [52]. In fact, it may reverse age induced bladder dysfunction. *In vivo* melatonin administration has also been demonstrated to have a protective property on the rat bladder after oxidative stress [53].

As stated previously, melatonin inhibits smooth muscle contractility directly. On a study that evaluated its effect on isolated guinea pig urinary bladder detrusor strips, and through its calcium channel blocking characteristic, melatonin was able to bind to Ca^{2+}-activated calmodulin with high affinity, and hinder myosin light chain kinase activation. As a result, on one hand, it maintains normal bladder contractile response through its antioxidant activity, and on the other hand, decreases contractility by affecting calcium channels [7].

As aging occurs, detrusor strips will gradually lose their sensitivity to cholinergic and purinergic agonists and membrane depolarization. This insensitivity correlates with an increased level of cytoplasmic calcium concentration $[Ca^{2+}]_i$ in response to the stimuli. Melatonin normalizes this impairment by re-adjustment of Ca^{2+} handling [54].

Melatonin and Acute and Chronic Detrusor Overactivity Models

In acute detrusor overactivity, melatonin does not significantly affect any of the urodynamic parameters. In urodynamic studies recorded in chronic detrusor overactivity, however, it is associated with an increase in intercontraction interval, increased bladder capacity, and an increase in threshold pressure [55]. These effects are due to melatonin's antioxidative function and not through its receptors because administering agomelatine, an antidepressant with melatonergic activity, deteriorates bladder dysfunction. However, this may not be the only reason behind agomelatine's action on the bladder. It may induce bladder overactivity by its 5HT2C receptor antagonism. Also, peripheral melatonin administration results in more antioxidative effects without involving the receptor [55].

Melatonin and Inflammation

Inflammatory processes can enhance bladder afferent pathway activation by inducing many stimulatory molecules (cyclooxygenases, prostaglandins and nerve growth factor, etc.). Also, the presence of pro-inflammatory cytokines such as interleukin-8, and TNF-α in inflammatory processes in bladder ischemia may indicate the formation of ROS [56]. These cytokines will, in turn, induce iNOS expression [57]. So, iNOS expression is associated with bladder inflammation. Interestingly, iNOS inhibitors diminish the symptoms of cystitis. It is believed that melatonin treatment suppresses iNOS expression [58].

Melatonin treatment attenuates the severity of cyclophosphamide-induced cystitis, as shown by reducing the increase in urinary frequency and the number of low volume voids. Microscopic examination of the histological appearance with hematoxylin and eosin staining of bladders after cyclophosphamide-treatment shows extensive cystitis with significant leukocytic infiltration occuring in the submucosa. In contrast, in melatonin-treated bladders, the urothelium appears to be well preserved, and inflammatory changes in the suburothelium are mitigated. These results indicated that melatonin treatment mitigates the severity of the inflammation induced by cyclophosphamide. More specifically, mast cell proliferation and activation are significantly increased in rats with cystitis following cyclophosphamide treatment or other stresses like water avoidance [59], and are markedly decreased by melatonin treatment [58]. Also, there is a decrease in expression levels of pro-inflammatory cytokines, TNF-α and IL-1β, after melatonin treatment.

There is a trend toward increasing HO-1 expression, the rate-limiting step in heme catabolism, in the bladders of rats with cyclophosphamide pretreatment. HO-1 is considered as a negative regulator of inflammation and oxidative stress, and also has potential neuroprotective effects against oxidative injury, all of which are associated with downregulation of iNOS expression [60, 61]. Melatonin is cytoprotective by upregulating HO-1 and downregulating iNOS expression in the bladder under oxidative stress. Another marker is substance P which increases significantly in the spinal cord after chronic cyclophosphamide-induced cystitis, and is decreased markedly after melatonin administration. Thus substance P release which increases in L6–S1 spinal cord under the condition of chronic cystitis, will decrease after melatonin treatment [58].

Similar to its previously mentioned effect on chronically overactive bladders, melatonin reduces the detrusor motor overactivity in inflamed bladders, resulting in the improvement of cystometric parameters as follow: a significant increase of intercontraction interval and functional bladder capacity, as well as a decrease of the basal pressure. Autonomic nervous system activity analysis shows sympathetic overactivity in hyperosmolar-induced overactive bladder rats, which is inhibited by melatonin treatment [62].

Conclusion

Although the exact mechanisms of action of melatonin on bladder function is yet to be fully understood, there is a strong body of evidence suggesting that its imbalance has a detrimental effect on bladder dysfunction.

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