Journal of Critical Care (2010) **25**, 656.e1–656.e6

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Journal of Critical Care

Melatonin in septic shock: Some recent concepts☆

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Keywords:
Melatonin;
Septic shock;
Antioxidants;
Cytokines;
Nitric oxide

Abstract Melatonin is a versatile molecule, synthesized not only in the pineal gland, but also in many other organs. Melatonin plays an important physiologic role in sleep and circadian rhythm regulation, immunoregulation, antioxidant and mitochondrial-protective functions, reproductive control, and regulation of mood. Melatonin has also been reported as effective in combating various bacterial and viral infections. Melatonin is an effective anti-inflammatory agent in various animal models of inflammation and sepsis, and its anti-inflammatory action has been attributed to inhibition of nitric oxide synthase with consequent reduction of peroxynitrite formation, to the stimulation of various antioxidant enzymes thus contributing to enhance the antioxidant defense, and to protective effects on mitochondrial function and in preventing apoptosis. In a number of animal models of septic shock, as well as in patients with septic disease, melatonin reportedly exerts beneficial effects to arrest cellular damage and multiorgan failure. The significance of these actions in septic shock and its potential usefulness in the treatment of multiorgan failure are discussed.

1. Introduction

Melatonin is a major secretory product of the pineal gland released every day at night. In all mammals, circulating melatonin is synthesized primarily in the pineal gland. In addition, melatonin is also locally found in various cells, tissues, and organs including lymphocytes, human and murine bone marrow, the thymus, the gastrointestinal tract, skin, and the eyes where it plays either an autocrine or paracrine role [1,2]. Both in animals and in human beings, melatonin participates in diverse physiologic functions, not only signaling

☆ Disclosure: SR Pandi-Perumal is a stockholder and the President and Chief Executive Office of Somnogen Inc, a New York corporation. He declared no competing interests that might be perceived to influence the content of this article. All remaining authors declare that they have no proprietary, financial, professional, or any other personal interest of any nature or kind in any product or services and/or company that could be construed or considered a potential conflict of interest that might have influenced the views expressed in this manuscript.

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doi:10.1016/j.jcrc.2010.03.006

the length of the night (and thus the time of the day or the season of the year) but also enhancing free radical scavenging, the immune response, and cytoprotective processes.

In several animal models, melatonin has been identified to protect against bacterial, viral, and parasitic infections presumably by acting through a variety of mechanisms, like immunomodulation or direct or indirect antioxidant activity [3]. Melatonin is a powerful antioxidant that scavenges superoxide radicals as well as other radical oxygen species (ROS) and radical nitrogen species and that gives rise to a cascade of metabolites that share its antioxidant properties. Melatonin also acts indirectly to promote gene expression of antioxidant enzymes and to inhibit gene expression of prooxidant enzymes [2].

Septic shock, the most severe problem of sepsis, is a lethal condition caused by a pathogen-induced long chain of sequential intracellular events occurring in immune cells, epithelium, endothelium, and the neuroendocrine system [4]. The lethal effects of septic shock are associated with the production and release of numerous proinflammatory biochemical mediators like cytokines, nitric oxide (NO), ROS, and radical nitrogen species radicals, together with development of massive apoptosis.

Melatonin has been shown to be beneficial for reversing symptoms of septic shock [5]. Melatonin had significant anti-inflammatory properties presumably by decreasing the synthesis of proinflammatory cytokines like tumor necrosis factor (TNF)–α and by suppressing inducible NO synthase (iNOS) gene expression. Melatonin also exerts a strong antiapototic effect [2]. This review article is focused on the significance of melatonin in septic shock and its potential utility to treat multiorgan failure. Published studies on animal models of inflammation and sepsis are summarized in Supplemental Tables 1 and 2.

In the next sections, we will review some of those studies with the aim of exemplifying the potential therapeutic use of melatonin in inflammation and septic shock.

2. Melatonin in lipopolysaccharide-induced inflammation

The first evidence for melatonin in controlling lipopolysaccharide (LPS)-induced damage was provided by Sewerynek and coworkers [6] in rats. They reported a reduction in LPS-induced oxidative insult after melatonin administration, as evidenced by decreased hepatic malondialdehyde (MDA) and 4-hydroxyalkenal (4-HDA) [6].

Melatonin prevents LPS-induced endotoxemia presumably by reducing circulating TNF-α levels, superoxide production in the aorta, and iNOS in the liver [7]. Melatonin (10-60 mg/kg) administered intraperitoneally (IP) to rats before and/or after LPS significantly decreased lung lipid peroxidation and counteracted the LPS-induced increase of NO levels in lungs and liver in a dose-dependent manner [8]. It also prevented LPS-induced metabolic alterations.

The activation of mitochondrial NOS can be a crucial trigger for initiation of the chain of events leading to septic shock [9]. The mitochondria express constitutive and inducible forms of NOS, the latter causing mitochondrial respiratory inhibition and failure. The protective role of melatonin against the enhancing effects of LPS on mitochondrial iNOS and the activity of respiratory complexes in liver and lung mitochondria were evaluated in young and old rats [10]. Melatonin administration (60 mg/kg, IP) effectively counteracted LPS-induced inhibition of complexes I and IV of the electron transport chain and decreased mitochondrial NOS activity and NO production, thereby preventing LPS toxicity [10]. The survival rate of LPS-injected mice improved from 0% in controls to 48% and 86% after melatonin administration (2 mg/kg) 3 and 6h later, respectively [11].

The effect of melatonin in preventing septic shock is complex. Apart from acting on the local sites of inflammation, melatonin also exerts its beneficial actions through a multifactorial pathway including its effects as immunomodulator, antioxidant, and antiapoptotic agent. This is exemplified by the study performed by Carrillo-Vico et al [12] in mice. It was reported that IP administered melatonin (10 mg/kg) 30 minutes before and 1 hour after LPS injection markedly protected the mice from the lethal effects of LPS with 90% survival rates for melatonin vs 20% in LPS-injected mice after 72 hours. Lipopolysaccharide induced the increase of nitrite/nitrate and lipid peroxidation levels in brain and liver. Melatonin administration increased the levels of the anti-inflammatory cytokine interleukin (IL)-10 and decreased the concentration of proinflammatory mediators like TNF-α, IL-12, and interferon-γ in the local site of LPS injection [12]. Morphologic evaluation of the apoptotic process showed that melatonin decreased the LPS-induced programmed cell death in spleen [12]. Melatonin's anti-apoptotic action was attributed to its stimulatory effect on IL-10 levels because IL-10 antiapoptotic action had already been demonstrated.

The effect of senescence on LPS-induced multiorgan failure and the efficacy of melatonin treatment to modify this condition were evaluated in rats [13]. Inducible NOS expression and activity, nitrite content, lipoperoxidation levels, and serum markers of liver, renal, and metabolic dysfunction were measured. An age-dependent increase in iNOS activity, NO content, and lipoperoxidation levels was observed; and these changes were augmented further by LPS [13]. Melatonin decreased the expression and activity of iNOS, reducing NO and lipoperoxidation levels to basal values in both LPS-treated groups. Liver, kidney, and metabolic dysfunctions were also significantly higher in aged rats and further increased by LPS. Melatonin treatment counteracted all these alterations in young and aged rats [13]. These findings are significant because the susceptibility of elderly patients to septic shock and multiorgan failure is

much greater than in young individuals. The alteration of the sleep/wake cycle may be one of the factors explaining this susceptibility in old individuals. Relevant to this, melatonin (5 mg/kg IP) attenuated the alveolar damage caused by LPS and counteracted the reduced levels of Bcl-XL and procaspase-3 seen in sleep-deprived mice [14]. Melatonin also prevented the increase of cell death and reduced the elevated higher levels of MDA in lungs of sleep-deprived mice [14].

It is well known that, during sepsis, ileus and mucosal cell barrier dysfunction occurs as one of its most frequent complications. Ileus, by promoting intestinal stasis, bacterial overgrowth, and bacterial translocation, may cause secondary infections and multiple organ failure. By using the LPS model, the beneficial effects of melatonin in preventing gastrointestinal disturbances were studied in mice [15]. Mice treated with LPS exhibited reduced gastric emptying of solid beads and altered distribution of glass beads throughout the gastrointestinal tract. Melatonin (10 mg/kg IP) reversed LPS-induced motility disturbances. Melatonin also normalized the altered lipid peroxidation, p38 mitogen-activated protein kinase activation, nuclear factor–κB activation, iNOS transcription and expression, and nitrite production in intestinal tissue from septic mice [15]. Melatonin is thus a molecule with therapeutic potential for the treatment of systemic inflammation because it interferes at the earliest step of activation of the oxidative and proinflammatory cascade. Melatonin and its metabolites may function as modulatory agents during the inflammatory process and have the potential to be a new class of anti-inflammatory agents with specificity for cyclooxygenase-2 and iNOS enzymes [16]. Melatonin treatment also reduced myeloperoxidase activity and MDA levels [17].

The possible protective effect of melatonin in LPS-induced pulmonary inflammation and lung injury was evaluated in rats [18]. Melatonin (10 mg/kg, IP) given 30 minutes before LPS prevented the decrease in Pao_2 and the lung injury caused by the endotoxin. Melatonin decreased pulmonary edema, the elevated lung myeloperoxidase (MPO) activity, and lipid peroxidation after LPS. The increase of the proinflammatory cytokine TNF-α levels in pulmonary tissue given by LPS was also prevented by melatonin, whereas the levels of the anti-inflammatory cytokine IL-10 were augmented. The decrease in LPS-induced pulmonary edema, lipid peroxidation, and the infiltration of neutrophils in lung tissue was interpreted in terms of the TNF-α inhibition and IL-10 stimulation brought about by melatonin [18].

Severe infection in diabetic patients often leads to multiorgan failure. In a study conducted to assess the protective effects of melatonin in LPS-injected rats turned diabetic by streptozotocin administration, LPS significantly increased the serum levels of TNF-α and IL-6 in normal and diabetic rats and augmented plasma corticotropin-releasing hormone, ACTH, and corticosterone [19]. Both 0.1- and 1-mg/kg melatonin doses significantly decreased serum levels of TNF-α and IL-6 in LPS-treated rats. Significant inhibitory effects of melatonin (1 mg/kg) were also observed on the hypothalamic-pituitary-adrenal axis [19]. Previous studies in diabetic rats indicated that melatonin was effective to restore normal vascular responses [20]. Therefore, melatonin treatment may help to prevent the vicious cycle of hyperglycemia and stress factors such as severe infection in diabetic patients.

3. Melatonin in non-LPS animals models of septic shock

Short-term melatonin administration (10 mg/kg IP) after hemorrhage significantly improved survival in animals subjected to a subsequent septic challenge by the cecal ligation and puncture (CLP) procedure [21]. In these mice, melatonin administration increased the survival rate by 28% as compared with vehicle-treated animals.

In another experimental model for septic shock, that is, the systemic administration of zymosan A that causes a massive release of proinflammatory mediators like TNF-α, IL-6, prostaglandins, NO, and ROS, a 100% mortality was observed, whereas the simultaneous administration of zymosan and melatonin (0.8 mg/kg) resulted in only 27% mortality rate [22].

The CLP model of sepsis was used to further understand the possible involvement of mitochondrial NOS and melatonin in the pathophysiology of sepsis by examining the changes in mitochondrial constitutive and iNOS activity and mitochondrial function in skeletal muscles of wild-type ($iNOS^{+/+}$) and iNOS knockout mice ($iNOS^{-/-}$) [23]. When 4 doses of melatonin (30 mg/kg) were injected IP in $iNOS^{+/+}$ mice, but not in $iNOS^{-/-}$ mice, sepsis increased mitochondrial NOS activity. Melatonin administration counteracted sepsis-induced mitochondrial iNOS activity in $iNOS^{+/+}$ mice, but did not affect mitochondrial constitutive NOS activity in either type of mice [23]. Mitochondrial nitrite significantly increased in $iNOS^{+/+}$ mice after sepsis, whereas melatonin treatment reduced nitrite levels to control values. Lipid peroxidation, which was increased in septic $iNOS^{+/+}$ mice, decreased significantly after melatonin administration. Sepsis significantly reduced the mitochondrial content of total glutathione (GSH) in $iNOS^{+/+}$ mice and increased the oxidized glutathione to GSH ratio, indicating a loss of reduced GSH. These changes in mitochondrial GSH pool during sepsis were counteracted by melatonin administration [23]. As far as the electron transport chain, complex I, II, II, and IV activities were significantly reduced in septic $NOS^{+/+}$ mice by about half; and the administration of melatonin not only prevented the inhibition of complex activities induced by sepsis but also increased their activities above their basal values [23].

Although extensively studied, the pathophysiology of sepsis-associated multiorgan failure remains undefined [4,24]. It has been proposed that a key defect in sepsis is

the disruption of oxidative phosphorylation within mitochondria [25]. The result is an inability of the cell to use molecular oxygen for adenosine triphosphate production, despite adequate oxygen availability. Melatonin normalized the production of adenosine triphosphate in $iNOS^{+/+}$ septic mice, without affecting $iNOS^{-/-}$ animals [26].

The efficacy of melatonin to prevent intraperitoneal sepsis and the associated multiple organ dysfunction syndrome was evaluated in rats subjected to the CLP procedure [27]. Melatonin was administered 3, 6, and 12 hours after CLP. The pressor response to norepinephrine was assessed at 0, 3, 9, and 18 hours after CLP surgery. Animals that received CLP alone showed a significantly progressive decrease in mean arterial blood pressure from 9 to 18 hours (ie, from about 120 to 70 mm Hg). In the animals that received CLP plus melatonin (0.3 mg/kg intravenously at 3 and 9 hours after CLP), the delayed fall in blood pressure was prevented [27]. The administration of melatonin completely restored the norepinephrine-induced vasomotor response back to normal. With regard to biochemical indexes of liver dysfunction, the rise in plasma glutamate-pyruvate transaminase and glutamate-oxaloacetate transaminase caused by CLP was prevented by melatonin treatment, as was the increase in creatinine, blood urea nitrogen, and lactate dehydrogenase (indicators of renal failure and cellular damage) in response to CLP [27].

Several cytokines released during sepsis, especially IL-1β, directly act on blood vessels, inducing vasodilatation through rapid production of platelet-activating factor and NO. In CLP rats, melatonin treatment diminished plasma NO and IL-1β concentrations, aortic superoxide levels, and the infiltration of polymorphonuclear neutrophils in lung and liver [27]. Therefore, Wu et al [27] attributed the beneficial effects of melatonin in the CLP septic model to inhibition of IL-β and NO production, O_2^- formation, and polymorphonuclear infiltration in organs. In a previous study, it had been observed that melatonin (10 mg/kg, IP) 30 minutes before and 6 hours after CLP counteracted the inhibition of in vitro ileal and bladder contractility caused by sepsis [28]. Considering that micromolar melatonin concentrations could be locally achieved through production by activated immune competent cells, extrapineal melatonin could have a protective effect against tissue injury in multiple organ dysfunction syndrome [29].

4. Melatonin studies in septic patients

Several studies have measured melatonin levels in critically ill patients to find out a possible correlation between melatonin and intensity of septic shock. In one of those studies carried out in intensive care unit (ICU) patients, 17 septic ICU patients, 7 ICU nonseptic patients, and 21 controls were examined [30]. 6-Sulfatoxymelatonin was determined in urine samples taken at 4-hour intervals over a total period of 24 hours. Urinary 6-sulfatoxymelatonin exhibited significant circadian periodicity in only 1 of 17 septic patients vs 6 of 7 in nonseptic patients and 18 of 23 in normal controls. The phase amplitude (an index of the maximal levels attained at peak concentrations) was significantly lower in septic patients. In sepsis survivors, 6-sulfatoxymelatonin excretion profiles tended to normalize, but still lacked a significant circadian rhythm at ICU discharge [30].

In another study, melatonin levels in blood and urine were studied over 3 consecutive days in 8 critically ill patients during deep sedation and mechanical ventilation at the ICU [31]. The circadian rhythm of melatonin release was abolished in all but one patient, who recovered much more quickly than the others [31].

Biochemical markers for the circadian rhythm were studied in 16 patients treated at the ICU of 2 regional hospitals in Sweden [32]. All urine excreted between 7:00 AM and 10:00 PM (day) and between 10:00 PM and 7:00 AM (night) was collected and sampled throughout the entire ICU period (median, 10 days) for the excretion of 6-sulfatoxymelatonin and free cortisol. Overall excretion of 6-sulfatoxymelatonin was lower and cortisol excretion was higher than reported for healthy reference populations [32]. Mechanical ventilation was associated with a markedly lower 6-sulfatoxymelatonin excretion (median, 198 ng/h) compared with periods without such help (555 ng/h), whereas infusion of adrenergic drugs increased 6-sulfatoxymelatonin excretion significantly. Five patients (31%) showed a virtually absent melatonin excretion for 24 hours or more. The diurnal rhythms were consistently or periodically disturbed in 65% and 75% of the patients [32].

Perras et al [33] measured serum melatonin concentrations at 2:00 AM in the first night in hospital in 302 patients consecutively admitted to the ICU. Correlations between illness severity (Acute Physiology and Chronic Health Evaluation II score and Therapeutic Intervention Scoring System) and melatonin levels were assessed. Overall analysis for the whole group of patients revealed no or very weak correlation between nocturnal serum melatonin levels and illness severity. In contrast, analysis of subgroups indicated that, in the 14 patients with severe sepsis, Acute Physiology and Chronic Health Evaluation and Therapeutic Intervention Scoring System scores were correlated negatively with nocturnal melatonin concentrations. In contrast, melatonin levels and illness severity were not correlated in patients admitted for coronary syndrome, intoxication, gastrointestinal bleeding, pneumonia, or stroke [33].

The alteration of the sleep-wake cycle, the augmented oxidative/nitrosative stress, and the altered inflammatory reaction seen in patients with septic shock render them suitable for melatonin therapy [34]. To assess in critically ill patients receiving mechanical ventilation the effect of exogenous melatonin on nocturnal sleep quantity, a randomized, double-blind, placebo-controlled trial including 24 patients who had undergone a tracheostomy was

performed [35]. Oral melatonin (10 mg) or placebo was administered at 9:00 PM for 4 nights. Nocturnal sleep was evaluated using the bispectral index (a signal-processing electroencephalographic technique). Actigraphy and subjective assessment of sleep were also used. Nocturnal sleep time was 2.5 hours in the placebo group, and melatonin use was associated with a 1-hour increase in nocturnal sleep [35]. Based on the supraphysiologic melatonin levels detected in plasma at the end of the night, the authors concluded that a lower amount of melatonin (1-2 mg) would probably be enough to improve sleep. However, amounts of melatonin in the 10-mg range or higher should be needed to warrant the effect on reduction of ischemic reperfusion injury, prevention of multiorgan failure, or treatment of sepsis.

From a different perspective, namely, to curtail oxidative stress, a number of clinical studies performed by Gitto and coworkers [36] have shown that melatonin reduces oxidative stress in newborns with sepsis, distress, or other conditions where there is excessive ROS production. In the first of these studies, a product of lipid peroxidation, MDA, and the nitrite/nitrate levels were measured in the serum of 20 asphyxiated newborns before and after treatment with melatonin given within the first 6 hours of life. Ten asphyxiated newborns received a total of 80 mg of melatonin (8 doses of 10 mg each separated by 2-hour intervals) orally. One blood sample was collected before melatonin administration, and 2 additional blood samples (at 12 and 24 hours) were collected after giving melatonin. Serum MDA and nitrite/nitrate concentrations in newborns with asphyxia before treatment were significantly higher than those in infants without asphyxia. In the asphyxiated newborns given melatonin, there were significant reductions in MDA and nitrite/nitrate levels. Three of the 10 asphyxiated children not given melatonin died within 72 hours after birth; none of the 10 asphyxiated newborns given melatonin died [36].

In a second study, a total of 20 mg melatonin was administered orally in 2 doses of 10 mg each with a 1-hour interval. The changes in the clinical status and the serum levels of the lipid peroxidation products MDA and 4-HDA were recorded in 10 septic newborns treated with the antioxidant melatonin given within the first 12 hours after diagnosis. Ten other septic newborns in a comparable state were used as "septic" controls, whereas 10 healthy newborns served as normal controls. Serum MDA + 4-HDA concentrations in newborns with sepsis were significantly higher than those in healthy infants without sepsis, and they were significantly reduced by melatonin. Melatonin also improved the clinical outcome of the septic newborns as judged by measurement of sepsis-related serum parameters after 24 and 48 hours [36].

Gitto et al also examined whether melatonin treatment would lower IL-6, IL-8, TNF-α, and nitrite/nitrate levels in 24 newborns with respiratory distress syndrome grade III or IV diagnosed within the first 6 hours of life. Compared with the melatonin-treated respiratory distress syndrome newborns, in the untreated infants, the concentrations of IL-6, IL-8, and TNF-α were significantly higher at 24 hours, 72 hours, and 7 days after onset of the study. In addition, nitrite/nitrate levels at all time points were higher in the untreated respiratory distress syndrome newborns than in the melatonin-treated babies. After melatonin administration, nitrite/nitrate levels decreased significantly, whereas they remained high and increased further in the respiratory distress syndrome infants not given melatonin.

Proinflammatory cytokines (IL-6, IL-8, and TNF-α) and the clinical status were examined in 110 preterm newborns with respiratory distress syndrome ventilated before and after treatment with melatonin. When comparing serum levels of IL-6, IL-8, and TNF-α for 2 groups, melatonin treatment clearly had anti-inflammatory effects [36]. In conclusion, these studies indicate that melatonin lowers IL-IL-6, IL-8, TNF-α, and nitrite/nitrate levels and modifies serum inflammatory parameters in surgical neonates, improving their clinical course.

5. Conclusion

Active research continues to define the principal alterations in sepsis, although significant challenges remain before this devastating process is understood and conquered. Melatonin has entered this arena because it has a promise as an appropriate add-on pharmacologic tool in sepsis. Although understanding of melatonin's action in the pathogenesis of septic shock is yet to be achieved, studies so far point out that melatonin, through its immunomodulatory, antioxidant, and antiapoptotic actions, may exert beneficial effects in septic shock and multiorgan failure. However, larger randomized controlled clinical trials are necessary to confirm the potential benefits of melatonin therapy before it can be routinely used in the postoperative or critically ill patients [37].

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jcrc.2010.03.006.

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